

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-725

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

14. Patent Certification

In the opinion and to the best knowledge of Solvay Pharmaceuticals, Inc. there are no patents that claim CREON® MINIMICROSPHERES® Capsules (Pancrelipase Delay-Release Capsules, USP) referred to in the application or that claim the treatment of exocrine pancreatic insufficiency in cystic fibrosis, chronic pancreatitis and post-surgery patients for CREON® MINIMICROSPHERES® Capsules.

This NDA is being submitted in response to FDA's 1991 Notice of Proposed Rulemaking, which withdrew the proposal for establishment of an OTC monograph for exocrine pancreatic insufficiency drug products and established that all exocrine pancreatic insufficiency drug products required an approved NDA for continued marketing.

Solvay Pharmaceuticals, Inc., introduced the CREON® microsphere product to the US market in 1987. In 1993, the microsphere product was replaced with the MINIMICROSPHERES® product in the US. The MINIMICROSPHERES® product is available in three strengths as CREON® 5, CREON® 10 and CREON® 20 capsules representing 5,000, 10,000 and 20,000 units of labeled lipase activity, respectively. The MINIMICROSPHERES® used in the manufacture of all of these drug product strengths are identical.

REQUEST FOR THREE YEAR EXCLUSIVITY

In accordance with the provisions of 21 CFR 314.108(b)(5), Solvay Pharmaceuticals, Inc. requests three years of exclusivity for the prescription marketing of CREON® MINIMICROSPHERES® Capsules (Pancrelipase Delay-Release Capsules, USP) in the treatment of exocrine pancreatic insufficiency in cystic fibrosis, chronic pancreatitis and post-surgery patients. 21 CFR 314.108(b)(5) states that three years of exclusivity will be granted for applications which contain reports of new clinical investigations conducted by the applicant and essential to the supplemental application.

To assist the Agency in determining which applications meet the three criteria for three years of exclusivity, we are providing the following information in this request as required by 21 CFR 314.50(j).

1. Whether a drug product containing all the same active ingredients with the same conditions of approval has been previously approved.

Solvay Pharmaceuticals, Inc. is aware of NDA 20-580, submitted by Organon, for the same drug substance utilized in the manufacture of Cotazym (immediate release containing 8,000 USP lipase units, 30,000 USP protease units, and 30,000 USP amylase units per capsule). This NDA was approved on December 9, 1996 with an indication for the treatment of steatorrhea due to exocrine pancreatic deficiency in such conditions as cystic fibrosis and chronic pancreatitis.

CREON® MINIMICROSPHERES® Capsules (Pancrelipase Delayed-Release Capsules, USP) differ from Cotazym in the content of lipase, protease and amylase units. CREON® 5 Capsules contain 5,000 USP lipase units, 16,600 USP amylase units, and 18,750 USP protease units; CREON® 10 Capsules contain 10,000 USP lipase units, 33,200 USP amylase units, and 37,500 USP protease units; CREON® 20 Capsules contain 20,000 USP lipase units, 66,400 USP amylase units, and 75,000 USP protease units.

CREON® MINIMICROSPHERES® also contain enteric coated delayed release MINIMICROSPHERES® of pancrelipase USP which resist gastric inactivation. The MINIMICROSPHERES® formulation are sized to produce homogenous mixing with chyme as it is released into the duodenum. Once in the duodenum, the enteric coating dissolves in response to the increased pH (5.5 or greater) and the enzymes are released to aid in digestion. The enteric coated MINIMICROSPHERES® formulation also differentiates the CREON® product from the Cotazym product.

We are requesting an indication for the treatment of adult and pediatric patients with exocrine pancreatic insufficiency as is often associated with, but not limited to, cystic fibrosis, chronic pancreatitis, post-pancreatectomy, post-gastrointestinal bypass surgery (e.g., Billroth II gastroenterostomy), and ductal obstruction of the pancreas or common bile duct (e.g., from neoplasm).

2. For purposes of exclusivity determinations, the Agency interprets the phrase "new clinical investigations" to mean investigations conducted on humans that have not been used by the Agency as part of the basis for a finding of substantial evidence of effectiveness for any previously approved new drug application or supplement.

The application contains the following new clinical investigations for CREON® MINIMICROSPHERES® to support the treatment of exocrine pancreatic insufficiency in cystic fibrosis, chronic pancreatitis and in post-surgery patients.

Three pivotal well controlled clinical studies:

Protocol	Indication	Section	Page
S2232101	cystic fibrosis	8.4.2.1.1	1029 -1120
S2232102	cystic fibrosis	8.4.2.1.1	2908 - 3019
223.201	chronic pancreatitis	8.4.2.1.2	5203 - 5301

Two supportive clinical studies:

Protocol	Indication	Section	Page
K245.5005	chronic pancreatitis	8.4.2.1.2	6455 - 6533
K245.5002	cystic fibrosis	8.4.2.2.1	7496 - 7586

Three clinical pharmacology studies:

Protocol	Indication	Section	Page
KREO 629	cystic fibrosis	8.3.3.1	47 - 96
S. Koletzko	cystic fibrosis	8.3.3.1	601 - 603
K224.5011	chronic pancreatitis	8.3.3.2	605 - 642

We certify that these studies have not been used as part of a finding of substantial evidence of effectiveness for a previously approved new drug application or supplement.

- 3. The Agency interprets the phrase "essential to approval" to mean that the application or supplement could not be approved without the investigation. If an abbreviated new drug application or new drug application described by section 505(b)(2) of the Act or supplement to either could have been approved for the drug product without the submitted studies, even with a delayed effective date, or if publicly available studies, other than those conducted or sponsored by the applicant, could have supported the application or supplement, then the investigation cannot be considered essential to the approval.**

A pre-NDA meeting to discuss CREON® was held on June 14, 1994. Also during a June 21, 1995 telephone call between Dr. Fredd, GI Division and Dr. Perkins, Solvay Pharmaceuticals, Inc., Dr. Fredd stated that the critical trials must be performed with the currently marketed product (CREON® MINIMICROSPHERES®), other trials which utilized the microspheres formulation would be considered supportive documentation of efficacy.

This application contains three pivotal clinical trials in exocrine pancreatic insufficiency that are essential to approval. These trials utilized the currently marketed MINIMICROSPHERES® formulation. Two clinical trials with the MINIMICROSPHERES® formulation, 11 clinical pharmacology studies (3 of which utilized the MINIMICROSPHERES® product) and sixty-eight clinical trials (including Solvay-sponsored trials and literature publications) with the microsphere formulation are provided as supportive data.

Tables 8.3.2.1, 8.3.2.2, 8.4.1, 8.5.1, 8.6.1.1 and 8.6.1.2 contain a list of all studies and publicly available reports of clinical investigations known to Solvay Pharmaceuticals, Inc. We certify that we have thoroughly searched the scientific literature from 1982 to 1997, and that the list of published studies and publicly available reports provided is complete to the best of our knowledge. We also certify that, in our opinion, published studies regarding CREON® MINIMICROSPHERES® or publicly available reports of clinical investigation (other than those sponsored by Solvay Pharmaceuticals, Inc., are not sufficient to support the approval of the use of CREON® MINIMICROSPHERES®.

4. The Agency considers an investigation to have been conducted or sponsored by the applicant if, before, or during the investigation, (1) the applicant was the sponsor named in the Form FDA 1571 (IND) for the investigation, or the (2) the applicant, or another entity the applicant purchased or merged with, provided substantial financial support for the investigation.

The efficacy of CREON® MINIMICROSPHERES® was demonstrated in three pivotal well-controlled clinical trials, Protocol S2233101 and S2233102 conducted in cystic fibrosis patients and Protocol 223.2.01 conducted in chronic pancreatitis patients which were conducted under IND 47,546. Solvay Pharmaceuticals, Inc., was the sponsor named in this IND. In addition, Solvay Pharmaceuticals, Inc. provided the financial support for the conduct of these clinical studies.

TABLE 8.3.2.1.
CREON® Clinical Pharmacology Studies - Cystic Fibrosis
Microspheres and MINIMICROSPHERES® Formulations

Study # and/or Investigator	Method/ Objective	Design	Blind	Control	Active Compound	Treatment Duration	CREON® Lipase Units	Lipase Units per Dose	N CREON®	N Placebo	Healthy Control Group
KREO 629*	¹⁴ C ₀ , Breath Test/ Correlation with Total Fat Excretion	Sequential	Double-blind	Placebo	-	6 Days	10,000	1,500/kg	11	11	12
S. Koletzko*	¹⁴ C ₀ , Breath Test/ Kinetics of Lipase Release	Single Treatment	Open-label	None	-	1 Day	25,000	25,000	9	-	10
S. Seal	¹⁴ C ₀ , Breath Test/ Site of Action	Crossover	Open-label	Active	Pancrease® HL	1 Day	8,000 25,000	8,000 or 25,000	18	-	-
O. Dewit	¹⁴ C ₀ , Breath Test/ Measure Starch Digestion	Crossover	Open-label	None	-	1 Day	8,000	48,000-80,000	5	-	8
V.T. Tsang	Effect of Enzyme Supplementation (± ranitidine) on Cyclosporin PK	Crossover	Open-label	Active	Cyclosporin A Ranitidine	1 Week	8,000	16,000-32,000	7	-	3**

* Trial performed with US-marketed MINIMICROSPHERES® formulation.
** Non-cystic fibrosis heart-lung transplant patients.

TABLE 8.3.2.2.
CREON® Clinical Pharmacology Studies - Chronic Pancreatitis
Microspheres and MINIMICROSPHERES® Formulations

Study # and/or Investigator	Method/ Objective	Design	Blind	Control	Active Compound	Treatment Duration	CREON® Lipase Units	Lipase Units per Dose	N CREON®	N Placebo	Healthy Control Group
K.224.5011*,†	¹⁴ CO ₂ Breath Test	Crossover	Double-blind	Placebo	-	1 Day	25,000	50,000	4	4	7
RR1044-04	Triple Lumen Technique/ Enzyme Delivery	Crossover	Double-blind	Placebo, Active	Pancrease®	10 Days	8,000	32,000	10	10	-
P. Kuhnelt	¹⁴ CO ₂ Breath Test Effect of Microsphere Size on Lipase Activity	Crossover	Double-blind	None	-	1 Day	5,000	50,000	10	-	11
KREO 916 P. Layer	Duodenal Delivery Time Comparing Microsphere Size	Crossover	Double-blind	None	-	1 Day (each formulation)	10,000	10,000	5	-	-
L. Guarner	Small Bowel Intubation Enzyme Activity	Crossover	Open-label	Placebo	-	1 Day (perfusion) 5 Day (fecal fat)	8,000	40,000	8	8	9
Norregaard**	Kinetics of Lipase Release	Single Dose	Open-label	None	-	1 Day	8,000	8,000	7	-	-

* Trial performed with US-marketed MINIMICROSPHERES® formulation.
** Half of granules replaced with radiolabeled particles.
† Study terminated early due to low enrollment and drug expiration.

TABLE 8.4.1.
CREON® MINIMICROSOPHERES® Formulation
All Clinical Trials

Study # and/or Investigator and/or Lit. Citation ¹	Patient Population	Design	Blinding	Control Type	Active Compound (other PERT ²)	Active Treatment Duration ³	CREON® (declared lipase units)	Age Range (mean)	Sex	Dose Caps/day	N ⁴ CREON®	N ⁴ Placebo	N ⁵ Active (other PERT)
CONTROLLED TRIALS													
Cystic fibrosis													
S2233101 ¹	Cystic fibrosis	Parallel	Double-blind	Placebo	—	4 weeks	20,000 USP	7-17 (12.5)	18M 20F	13.3 mean	18	20	
S2233102 ¹	Cystic fibrosis	Parallel	Double-blind	Placebo	—	4 weeks	20,000 USP	18-53 (23.8)	22M 14F	12.5 mean	18	18	
Chronic pancreatitis													
223.2.01 ¹	Chronic pancreatitis	Parallel	Double-blind	Placebo	—	2 Weeks	10,000 USP	31-74 (51.4)	18M 9F	12.5 mean	13	14	
K.245.5005 ¹	Chronic pancreatitis	Parallel	Double-blind	Placebo	—	3 Weeks	10,000 Ph. Eur.	39-68 (53.4)	31M 2F	16	17	16	
UNCONTROLLED TRIALS													
Cystic fibrosis													
K.245.5002 ¹	Cystic fibrosis	Crossover	Open-label	Active	Creon 12,000	4 weeks	10,000 USP	3-25	41M 28F	9.3 (mean)	69		69

¹ Investigators participating in more than one study are identified by literature citation.
² Pancreatic Enzyme Replacement Therapy.
³ Minimum planned sum total of treatment exposure.
⁴ Total treatment group numbers retrieved from clinical reports/publications and represents population after randomization.
⁵ Trials available in electronic format (ISS).

TABLE 8.5.1.
CREON® Microspheres Formulation
All Clinical Trials

Study # and/or Investigator and/or Lit. Citation ¹	Patient Population	Design	Blinding	Control Type	Active Compound (other PERT ²)	Active Treatment Duration ³	CREON® (declared lipase units)	Age Range (mean)	Sex	Dose Caps/day	N ⁴ CREON®	N ⁴ Placebo	N ⁴ Active (other PERT)
CONTROLLED TRIALS													
Cystic Fibrosis													
CREON 8402 ⁵	Cystic fibrosis	Crossover	Double-blind	Active	Pancrex V Forte	8 Weeks	8,000 USP	4-15 (9.6)	Not stated	13 median	20	---	20
KREO 586 ⁵	Cystic fibrosis	Crossover	Double-blind	Active	Pancrease	10 Weeks	8,000 FIP	5.9-18.3 (10.3)	12M 15F	16.3 mean	27	---	27
K 224-5001 ⁵	Cystic fibrosis	Crossover	Double-blind	Active	Panzytrat	8 Weeks	25,000 USP	3-29 (11.7)	42M 46F	6.3 mean	88	---	88
J. Williams	Cystic fibrosis	Crossover	Single-blind	Active	Pancrease	8 Weeks	8,000 BP	5-17 (9.7 median)	Not stated	20 median	39	---	39
S. Regele ⁶	Cystic fibrosis	Crossover	Double-blind	Active	Panzytrat	8 Weeks	25,000 FIP	3-27 (9.9)	7M 9F	Not stated	16	---	16
Chronic pancreatitis													
RR 1044-03 ⁵	Chronic pancreatitis	Crossover	Double-blind	Placebo	---	8 Weeks	8,000 USP	Not stated	Not stated	12	53	53	---
KREO 628 ⁵	Chronic pancreatitis	Crossover	Double-blind	Placebo	---	8 Weeks	10,000 Ph. Eur. (41.7)	28-51 (41.7)	14M 17F	10-20	27	29	---
M. Latvin	Chronic pancreatitis	Crossover	Double-blind	Placebo	---	8 Weeks	Not stated	Not stated	Not stated	12	78	78	---

¹ Investigators participating in more than one study are identified by literature citation.
² Pancreatic Enzyme Replacement Therapy.
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⁵ Trials available in electronic format (ES).
⁶ Single-center data from K.224-5001 published separately by this investigator.

(Continued)

TABLE 8.5.1.
CREON® Microspheres Formulation
All Clinical Trials

Study # and/or Investigator and/or Lit. Citation ¹	Patient Population	Design	Blinding	Control Type	Active Compound (other PERT)	Active Treatment Duration ²	CREON® (declared lipase units)	Age Range (mean)	Sex	Dose Capsul/day	N ³ CREON®	N ⁴ Placebo	N ⁴ Active (other PERT)
CONTROLLED TRIALS													
Chronic pancreatitis (continued)													
K. 224.5003 ⁵	Chronic pancreatitis	Crossover	Double-blind	Active	Pancrease	5 Weeks	25,000 Ph. Eur.	23-58 (45.5)	7M 4F	16.6 mean	11	---	11
P.G. Lankisch Z. Gastroenterologie 1986;24:733-757	Chronic pancreatitis	Crossover	Single-blind	Active	Pancreon 700 Cimetidine	9 Days	10,000 FIP	Not stated	7M 1F	18	8	---	8
Ch. Kolbel	Chronic pancreatitis	Crossover	Single-blind	Placebo	---	13 Days	10,000 FIP	Not stated	10M 1F	5 x 3 days 10 x 5 days 15 x 3 days	11	11	11
Postsurgery													
NK. 223.00.02 ⁵	Postsurgical	Parallel	Single/ Double-blind	Placebo	---	8 Weeks	8,000 USP	44-62 (33.2)	10M 5F	Sgl-blind 5.4 Dbl-blind 4.9	15	8	---
K. 224.5003 ⁵	Postsurgical	Crossover	Double-blind	Active	Creon 8	6 Weeks	25,000 FIP	26-79 (51.7)	28M 11F	19.4 mean	39	---	39
Other													
KREO.602 (K. Rossmann)	Acute pancreatitis	Parallel	Double-blind	Placebo	---	2-3 Weeks	20,800 FIP	Not stated	Not stated	3-6 granule bags/day	20	20	20
M.J. McMahon	Acute pancreatitis	Parallel	Double-blind	Placebo	---	6 Weeks	Not Stated	Not stated	Not stated	14	21	20	20
R.V. Patankar	Acute pancreatitis	Parallel	Double-blind	Placebo	---	5-10 Days	8,000 BP	29-86 (67 median)	13M 14F	12	9	14	14
U. Ambrecht	Postsurgical (total gastrectomy)	Crossover	Double-blind	Placebo	---	1 Week	10,000 FIP	47-83 (64)	10M 5F	12	15	15	15

1 Investigators participating in more than one study are identified by literature citation.
 2 Pancreatic Enzyme Replacement Therapy
 3 Maximum planned sum total of treatment exposure
 4 Total treatment group numbers retrieved from clinical reports/publications and represents population after randomization.
 5 Trials available in electronic format (ISS)

(Continued)

TABLE 8.5.1.
CREON® Microspheres Formulation
All Clinical Trials

Study # and/or Investigator and/or Lit. Citation ¹	Patient Population	Design	Blinding	Control Type	Active Compound (other PERT ²)	Active Treatment Duration ³	CREON® (declared lipase units)	Age Range (mean)	Sex	Dose Caps/ day	N ⁴ CREON®	N ⁴ Placebo	N ⁴ Active (other PERT)
UNCONTROLLED TRIALS													
Cystic fibrosis													
223.8.01 ⁵	Cystic fibrosis	Crossover	Open	Active	Creon 8	5 Weeks	25,000 USP	6-21 (12.8)	17M 16F	3-21	33	-	33
KREO 584 ⁵	Cystic fibrosis	Single arm	Open	Historical	-	2 Years	8,000 Ph. Eur.	3-14 (10)	15M 14F	3-16	29	-	-
CREON 8403 ⁵	Cystic fibrosis	Crossover	Open	Active	Pancrex V forte	8 Weeks	8,000 USP	17-31 (24)	Not stated	17 median	21	-	21
K.224.5010 ⁵	Cystic fibrosis	Crossover	Open	Active	Cotazym 5 Forte	8 Weeks	25,000 USP	3-16 (8.7)	9M 5F	9 median	14	-	14
K.224.5006 ⁵	Cystic fibrosis	Crossover	Open	Active	CREON® 8 Pancrease	26 Weeks	25,000 USP	1.5-16 (7.1)	25M 20F	17.8 mean	45	-	47
KREO 510	Cystic fibrosis	Crossover	Open	Active	Pankreon forte	8 Weeks	8,000 FIP	4-20 (11.8)	20F	5.1 mean	42	-	42
V.P. Abiodun	Cystic fibrosis	Crossover	Open	Active	Pankreon forte	33 Days	10,000 FIP	6.4-21.2 (12.3)	Not stated	5, 8, or 13	12	-	12
KREO 554 (Stead)	Cystic fibrosis	Crossover	Open	Active	Pancrex V forte	8 Weeks	8,000 BP	(24.8)	11M 12F	19 mean	23	-	23
D.W. Beverley	Cystic fibrosis	Crossover	Open	Active	Pancrease/ Pancrex V Fortal/ Pancreatin Merck	7 Weeks	8,000 BP	6-20 (12 = median)	Not stated	Not stated	19	-	19
KREO 522 - 527	Cystic fibrosis	Crossover	Open	Active	PME	1-26 Weeks	8,000 BP	2-17 (8.9)	21M 21F	≤ 8	44	-	44
KREO 541	Cystic fibrosis	Crossover	Open	Active	Pancrease	2 Weeks	Not stated	3-12 (7)	10M 6F	9 mean	16	-	16
G. Morrison Alimont Pharmacol Thera 1992;6:549-555	Cystic fibrosis	Crossover	Open	Active	Pancrease HI	4 Weeks	8,000 BP	1-27 (8 = median)	18M 15F	≥ 12	38	-	38

¹ Investigators participating in more than one study are identified by literature citation.
² Pancreatic Enzyme Replacement Therapy
³ Maximum planned sum total of treatment exposure
⁴ Total treatment group numbers retrieved from clinical reports/publications and represents population after randomization.
⁵ Trials available in electronic format (ISS)

(Continued)

TABLE 8.5.1.
CREON® Microspheres Formulation
All Clinical Trials

Study # and/or Investigator and/or Lit. Citation ¹	Patient Population	Design	Blinding	Control Type	Active Compound (other PERT) ²	Active Treatment Duration ³	CREON® (declared lipase units)	Age Range (mean)	Sex	Dose Caps/day	N ⁴ CREON®	N ⁴ Placebo	N ⁴ Active (other PERT)
UNCONTROLLED TRIALS													
Cystic fibrosis													
G. Morrison Lancet 1991;338:1596-97	Cystic fibrosis	Crossover	Open	Active	Pancrease HL	8 Weeks	8,000 BP	Not stated	Not stated	24.9 mean	10		10
B. Gottschalk	Cystic fibrosis	Crossover	Open	Active	Panzylrat	10 Days	10,000 FIP	6-26	Not stated	3-12	10		10
P.L. Zentler-Munro	Cystic fibrosis	Crossover	Open	Placebo/active	Aspergillus niger lipase Pancrex	2 Weeks	8,000 BP	19-34	Not stated	6 per meal	10	10	10
V. Ziros	Cystic fibrosis	Crossover	Open	Active	Cotazym forte	8 Weeks	10,000 USP	4-13	5M 7F	4 mean	12		12
M. Stern Klin Padiatr. 1988;200:36-39	Cystic fibrosis	Crossover	Open	Active	Panzylrat	10 Days	10,000 FIP	2-24 (12.9)	11M 6F	6-15	17		17
RR 1044-01 ⁵ (George)	Cystic fibrosis	Crossover	Open	Active	Pancrease	3 Weeks	8,000 USP	3-27 (8.9)	10M 11F	9 mean	21		21
KREO.592 ⁵	Cystic fibrosis	Crossover	Open	Active	Creon Granules	12 Weeks	8,000 Ph. Eur.	0.4-12.1 (4.2)	6M 11F	29 mean	17		17
J.L. Murphy	Cystic fibrosis	Single arm	Open	Normal Healthy	—	52 Weeks	8,000 USP	5-25 (11.4)	7M 13F	22 mean	20		20
J. Henker Z Klin. Med. 1988;43(15):1331	Cystic fibrosis	Single arm	Open	Normal Healthy	—	40 Weeks	Not stated	5-20 (13)	10M 4F	Not stated	14		14
KREO.560	Cystic fibrosis	Single arm	Open	None	—	Not stated	Not stated	1-16	24M 14F	Not stated	38		38
G. Owen	Cystic fibrosis	Retro-spective	Open	Active	Pancrease	Not stated	Not stated	1-17.5 (8.4)	Not stated	23.9 mean	71		71
C.P. Berlin	Cystic fibrosis	Parallel	Open	Active	Pancrease	24 Weeks	10,000 FIP	< 10	Not stated	8	8		8
N. Kahrskaja	Cystic fibrosis	Single arm	Open	None	—	52 Weeks	Not stated	0-15	Not stated	Not stated	46		46
K 224 9004 I. Bowler	Cystic fibrosis	Crossover	Open (CREON)	Placebo/Active	Ramitidine	6 Weeks	25,000 USP	5.5-16.3 (11.9)	Not stated	Not stated	14	14	14

1 Investigators participating in more than one study are identified by literature citation.
2 Pancreatic Enzyme Replacement Therapy
3 Maximum planned sum total of treatment exposure
4 Total treatment group numbers retrieved from clinical reports/publications and represents population after randomization.
5 Trials available in electronic format (ISS)

(Continued)

TABLE 8.5.1.
CREON® Microspheres Formulation
All Clinical Trials

Study # and/or Investigator and/or Lit. Citation ¹	Patient Population	Design	Blinding	Control Type	Active Compound (other PERT ²)	Active Treatment Duration ³	CREON® (declared lipase units)	Age Range (mean)	Sex	Dose Caps/day	N° CREON®	N° Placebo	N° Active (other PERT)
UNCONTROLLED TRIALS													
Chronic pancreatitis													
P. Brackmann	Chronic pancreatitis	Crossover	Open	Active	Pankreon 700	2 Weeks	10,000 FIP	28-58 (44.2)	Not stated	3	20	-	20
KREO 542	Chronic pancreatitis	Crossover	Open	Active	Pankreon 700	2 Weeks	8,000 FIP	(46.4)	26M 4F	9	30	-	30
G. Backes	Chronic pancreatitis	Crossover	Open	Active	Kreon Granules	2-4 Weeks	10,000 FIP	Not stated	Not stated	6-9	12	-	12
KREO 537	Chronic pancreatitis	Crossover	Open	Active	Pankreon 700	2 Weeks up to 7 mos.	10,000 FIP	(47.2)	11M 1F	7	12	-	12
M.U. Schneider	Chronic pancreatitis	Crossover	Open	Active	Mortale/ Pankreon Granulatis	6 Weeks	10,000 FIP	Not stated	Not stated	10	17	-	17
F. Marotta	Chronic pancreatitis	Crossover	Open	Active	Viokase/ Pancrease/ Ranitidine+ Viokase	7 Days	8,000 BP	40-59 (49.4)	12M 0F	2 x 1 day then 6 x 3 days	12	-	12
J. Emerit	Chronic pancreatitis	Crossover	Open	Active	Eurobiol	12 Days	8,000 Ph. Eur.	22-78 (47)	26M 7F	≤ 9	33	-	33
I. Bero	Chronic pancreatitis/ pancreatic tumors	Crossover	Open	Active	Neopantpur	20 Days	8,000	32-69 (46.9)	14M 1F	6	15	-	15
M. J. Varas	Chronic pancreatitis	Crossover	Open	Active	Pankreon 700	2 Weeks	8,000 FIP	(50)	4M 0F	6	4	-	4
U N Francoual	Chronic pancreatitis and other disorders	Crossover	Open	Active	Eurobiol	8 Weeks	12,000 Ph. Eur	28-84 (52)	15M 42F	7.6 mean	200	-	200
B B Jørgensen	Chronic pancreatitis	Crossover	Open	Active	Pancrease/ Pancreatin	3 Weeks	8,000 FIP	34-73 (51 = median)	19M 5F	2/meal 1/snack	24	-	24

¹ Investigators participating in more than one study are identified by literature citation.

² Pancreatic Enzyme Replacement Therapy

³ Maximum planned sum total of treatment exposure

⁴ Total treatment group numbers retrieved from clinical reports/publications and represents population after randomization.

(Continued)

TABLE 8.5.1.
CREON® Microspheres Formulation
All Clinical Trials

Study # and/or Investigator and/or Lit Citation	Patient Population	Design	Blinding	Control Type	Active Compound (other PERT ¹)	Active Treatment Duration ²	CREON® (declared lipase units)	Age Range (mean)	Sex	Dose Capsul/day	N ³ CREON®	N ³ Placebo	N ³ Active (other PERT)
UNCONTROLLED TRIALS													
Chronic pancreatitis													
P.G. Lankisch 1988;113:15-17	Chronic pancreatitis	Crossover	Open	Active	Panzytrat	5 Days	10,000 FIP	33-57	9M 0F	18	9	--	9
KREO 901	Chronic pancreatitis	Single arm	Open	None	--	8 Weeks	10,000	40-62	7M 3F	6	10	--	10
KREO 605	Chronic pancreatitis	Single arm	Open	None	--	6 Days	10,000 FIP	Not stated	Not stated	16-18 caps or 3 x 3 bags	16	--	16
KREO 511	Chronic pancreatitis	Single arm	Open	None	--	14 Weeks	8,000	31-53 (42.5)	15M 0F	10 x 5 days 15 x 5 days 10 x 90 days	15	--	15
J. Simek Vnitřní Lekarství 1993;39(3):250-252	Chronic pancreatitis	Single arm	Open	None	--	30 Days	8,000 FIP	38-65	16M 4F	6-24	18	--	18
B. Lembcke	Chronic pancreatitis	Single arm	Open	None	--	5 Days	10,000 FIP	Not stated	Not stated	18	8	--	8
M. Vuoristo	Chronic pancreatitis	Single arm	Open	None	--	10-13 Weeks	8,000 Ph. Eur.	42-77 (62)	5M 3F	2-3 a meal	8	--	8
A. Pap Orvosi Hetilap 1990; 131(5):241-244	Chronic pancreatitis	Crossover	Open	Active	Panpur	5 Days	8,000	Not stated	Not stated	10 or 15	39	--	39
A. Pap Dig Diseases Sciences 1987;32(10):1182A	Chronic pancreatitis	Not stated	Open	Active	Panpur	Not stated	8,000	Not stated	Not stated	Not stated	15	--	15
M. Dellhaye	Chronic pancreatitis	Crossover	Open	Active	CREON® 8000/ Pancrease HL + omeprazole	8 Weeks	8,000 EPU	40-69 (52.4)	24M 1F	3/meal	25	--	25
H. Biermann	Pancreatic insufficiency & toxic alcoholic liver damage	Crossover	Open	Active	Pankreon 700	20 Days	10,000 FIP	27-53 (44.3)	15M 1F	10	16	--	16

¹ Investigators participating in more than one study are identified by literature citation.

² Pancreatic Enzyme Replacement Therapy

³ Maximum planned sum total of treatment exposure

⁴ Total treatment group numbers retrieved from clinical reports/publications and represents population after randomization.

(Continued)

TABLE 8.5.1.
CREON® Microspheres Formulation
All Clinical Trials

Study # and/or Investigator and/or Lit. Citation ¹	Patient Population	Design	Blinding	Control Type	Active Compound (other PERT ²)	Active Treatment Duration ³	CREON® (declared lipase units)	Age Range (mean)	Sex	Dose Caps/ day	N ⁴ CREON®	N ⁴ Placebo	N ⁴ Active (other PERT)
UNCONTROLLED TRIALS													
Postsurgery													
P.M. Plinning	Postsurgical	Single arm	Open	Baseline	—	4 Days	10,000 FIP	34-66	7M 2F	10	9		
G. Bohl	Postsurgical	Single arm	Open	None	—	6 Weeks	10,000	3-15 (8.25)	31M 17F	3-6 mode	48		
Other Populations													
L. Gretzmacher	Upper GI complaints	Single arm	Open	None	—	4 Weeks	10,000 FIP	>50% >50 16.6% < 40 21.7% = 40-49	7582M 8129F	3-6	15/11		

1 Investigators participating in more than one study are identified by literature citation.
 2 Pancreatic Enzyme Replacement Therapy.
 3 Maximum planned sum total of treatment exposure.
 4 Total treatment group numbers retrieved from clinical reports/publications and represents population after randomization.

4 pp withheld in full immed. after this page as (b)(4) CCI/TS.

EXCLUSIVITY SUMMARY

NDA # 20725

SUPPL #

HFD #

Trade Name Creon

Generic Name pancrelipase

Applicant Name Solvay Pharmaceuticals, Inc.

Approval Date, If Known ~4/30/09

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-580

Cotazym

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

clinical trial Study S245.3.126 entitled "A Double-Blind, Randomized, Multi-Center, Placebo-Controlled, Cross-Over Study to Assess the Efficacy and Safety of Pancrelipase"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

clinical trial Study S245.3.126 entitled "A Double-Blind, Randomized, Multi-Center, Placebo-Controlled, Cross-Over Study to Assess the Efficacy and Safety of Pancrelipase"

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # 47,546 YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

!

NO

Explain:

Investigation #2

YES

Explain:

!

!

!

NO

Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Cristi Stark
Title: Senior Regulatory Health Project Manager
Date: 4/29/09

Name of Office/Division Director signing form: Donna Griebel, MD
Title: 4/29/09

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Donna Griebel
4/29/2009 12:17:58 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 20-725 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Gastroenterology PDUFA Goal Date: 3/20/09 Stamp Date: 6/20/2008
Products

Proprietary Name: Creon

Established/Generic Name: pancrelipase delayed-release

Dosage Form: capsules

Applicant/Sponsor: Solvay Pharmaceuticals, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input checked="" type="checkbox"/>	Neonate	0 wk. __ mo.	4 wk. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): not usually diagnosed before one month

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	12 yr. __ mo.	18 yr. __ mo.	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Other	0 yr. 1 mo.	16 yr. 11 mo.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

Cristi Stark
4/27/2009 10:26:23 AM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 20-725 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Gastroenterology PDUFA Goal Date: 3/20/09 Stamp Date: 6/20/2008
Products

Proprietary Name: Creon

Established/Generic Name: pancrelipase delayed-release

Dosage Form: capsules

Applicant/Sponsor: Solvay Pharmaceuticals, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input checked="" type="checkbox"/>	Neonate	0 wk. __ mo.	4 wk. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): not usually diagnosed before one month

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. 1 mo.	6 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	7 yr. __ mo.	11 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): 07/31/10 and 06/30/09 respectively							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: Note: after our PeRC meeting, it was decided that the label would be indicated for all pediatric ages. Even though we are using extrapolation for efficacy in the pediatric groups (as discussed at PeRC), the pediatric studies will still be deferred to fully inform the label for safety (note Section F is filled out but we will still defer the studies as a PREA PMR).

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	12 yr. __ mo.	18 yr. __ mo.	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. 1 mo.	11 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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this page is the manifestation of the electronic signature.**

/s/

Cristi Stark
3/9/2009 10:00:49 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 20-725 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 11/20/2006 PDUFA Goal Date: 5/18/2007

HFD 180

Trade and generic names/dosage form: Creon (pancrelipase) Capsule Delayed-Release

Applicant: SOLVAY Pharmaceuticals, Inc. Therapeutic Class: 8015616

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: indicated for the adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency.

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg 3.3 mo. 1 m yr. x Tanner Stage _____
Max _____ kg 59 mo. _____ yr. 17.6 Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 20-725

Page 3

This page was completed by:

{See appended electronic signature page}

Maureen Dewey, MPH
Regulatory Project Manager

{See appended electronic signature page}

Ethan D Hausman, M.D.
Medical Reviewer

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 - No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed
- NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

Maureen Dewey
4/4/2007 12:17:52 PM

Ethan Hausman
4/4/2007 12:27:13 PM

Anne Pariser
4/4/2007 12:56:09 PM

SOLVAY PHARMACEUTICALS, INC.

CREON® MINIMICROSPHERES®
(Pancrelipase Delayed-Release Capsules, USP)
NDA 20-725
Section 1

DEBARMENT CERTIFICATION STATEMENT

I hereby certify that Solvay Pharmaceuticals, Inc., did not and will not use in any capacity the services of any person debarred under Subsections 306(a) or 306(b) of the Federal Food, Drug, and Cosmetic Act in connection with New Drug Application 20-725 dated July 31, 1997, for CREON® MINIMICROSPHERES® (Pancrelipase Delayed-Release Capsules, USP). [Section 306(k)(1) of the Generic Drug Enforcement Act (21 USC 335a(k)(1))].



J. Greg Perkins, Ph.D., Senior Vice President
Regulatory and Quality Systems

MEMORANDUM OF TELECON

DATE: April 30, 2009

APPLICATION NUMBER: NDA 20725

BETWEEN:

Name: Don Ruggirello
Senior Director, Regulatory Affairs
Phone: 770-578-5658
Representing: Solvay Pharmaceuticals, Inc.

AND

Name: Elizabeth A.S. Ford, R.N.
Regulatory Health Project Manager
Division of Gastroenterology Products, HFD-180

SUBJECT: NDA 20-725, PMR-PMC Timetable: April 17, 2009 submission

This teleconference was held to discuss the postmarketing requirement (PMR) and postmarketing commitment (PMC) timetables submitted to NDA 20-725 on April 17, 2009. The FDA requested Solvay Pharmaceuticals Inc. (Solvay) identify a Study Completion Date for the following PMRs:

- A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with CREON in the US and to assess potential risk factors for the event.

The timetable you submitted on April 17, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	June 20, 2010
Study Start Date:	January 1, 2011
Final Report Submission:	June 20, 2021

- A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking CREON.

The timetable you submitted on April 17, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	June 20, 2010
Study Start Date:	January 1, 2011
Final Report Submission:	June 20, 2021

In addition, the FDA requested Solvay identify a Final Protocol Submission Date for the following PMC:

- Solvay commits to perform routine monitoring of the enveloped viral load entering the manufacturing process. The control strategy will include the selection of human pathogenic enveloped viruses for monitoring by qPCR together with action limits and specifications.

Protocol Submission: by October 20, 2009

Final Report Submission: by October 20, 2010

Solvay indicated the requested dates would be identified in follow up correspondence to the Regulatory Health Project Manager (RPM). The call concluded at 11:00 AM. The follow up correspondence, sent electronically to the RPM, indicated a study completion date of January 1, 2021 for the two PMRs identified in this memorandum. In addition, Solvay confirmed that the PMC "Protocol Submission" date, for the above-mentioned PMC, is in fact the "Final Protocol Submission" date. The relevant correspondence is provided as attachment 1 and attachment 2 to this memorandum.

SIGNER'S NAME
TITLE

Attachment 1: Email correspondence from Don Ruggirello to Elizabeth Ford

From: Ruggirello, Don [Don.Ruggirello@solway.com]
Sent: Thursday, April 30, 2009 11:23 AM
To: Ford, Elizabeth
Cc: Allgood, Adam; Horton, Rex; Braband, Walt
Subject: Updated PMRs/PMCs per your request

Attachments: PMC Submission (2).doc

Elizabeth,

In response to your request, I have update the PMRs/PMCs accordingly. The updates are highlighted in yellow.

Don

Don Ruggirello
Senior Director, Regulatory Affairs
Phone: 770-578-5658
Cell: 404-307-8532
FAX- 770-578-5864
Don.Ruggirello@solway.com

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Merci d'informer immediatement l'expediteur par messagerie electronique et d'ensuite detruire ce message.

Attachment 2: Attachment identified as “PMC Submission (2).doc” in email correspondence dated April 30, 2009 between Don Ruggirello and Elizabeth Ford (cited as Attachment 1 in this memorandum).

For CREON NDA 20-725, the following are Solvay Pharmaceuticals Inc.’s postmarketing commitments subject to reporting requirements under 21 CFR 314.81 and Solvay Pharmaceuticals Inc.’s postmarketing requirements under Title IX, Subtitle A, Section 901 of the 2007 FDAAA:

1. Solvay is required to conduct a 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with CREON in the US and to assess potential risk factors for the event.

Final Protocol Submission by: June 20, 2010
Study Start Date by: January 1, 2011
Study Completion date by: January 1, 2021
Final Report Submission by: June 20, 2021

2. Solvay is required to conduct a 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking CREON.

Final Protocol Submission by: June 20, 2010
Study Start Date by: January 1, 2011
Study Completion date by: January 1, 2021
Final Report Submission by: June 20, 2021

3. Solvay commits to complete Study S245.3.124, a multi-center, randomized, double-blind, placebo-controlled trial of the safety and effectiveness of CREON in patients 18 years and older with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy. The study will have an open-label 6-month extension.

Final Report Submission by: September 20, 2009

4. Solvay commits to perform routine monitoring of the enveloped viral load entering the manufacturing process. The control strategy will include the selection of human pathogenic enveloped viruses for monitoring by qPCR together with action limits and specifications.

Final Protocol Submission by: October 20, 2009
Final Report Submission by: October 20, 2010

5. Solvay commits to develop sensitive qPCR assays that provide adequate assurance that process capability for the inactivation of non-enveloped viruses is not exceeded.

**Revised Assay, Assay Validation Data and New Action Limits Submission by:
October 20, 2009**

6. Solvay commits to develop and implement specifications for infectious porcine circoviruses (PCV) 1 and 2 in the drug substance. The proposed methods, including relevant method validation, will be submitted to the Agency.

Methods Submission by: October 20, 2009

Final Specifications Implemented by: October 20, 2010

7. Solvay commits to assess the risk to product quality associated with porcine hokovirus, and submit a control strategy for mitigating this risk to product quality.

Final Risk Assessment and Control Strategy Submission by:

October 20, 2009

8. Solvay commits to revise the acceptance criteria for the viral infectivity tests for swine vesicular disease virus (SVDV), encephalomyocarditis virus (EMCV) and porcine rotavirus (Rota) to “none detected.”

Revised Acceptance Criteria Submission by: July 1, 2009

9. Solvay commits to provide detailed plans for its animal disease surveillance program and continued risk assessment evaluation for source animals. The proposed plans will include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these plans will be implemented.

Final Plans Submission by: October 20, 2009

10. Solvay commits to assess the risk to product quality due to the potential infection of swineherds with parasites.

Final Risk Assessment and Control Strategy Submission by:

October 20, 2009

11. Solvay commits to provide a detailed description of its plans for preventing cross-contamination with material from other species, particularly with ruminant tissues.

Final Plans Submission by: October 20, 2009

12. Deferred requirement for development of age appropriate formulation under PREA: Develop an age appropriate formulation. The age appropriate formulation needs to be adequate to allow for dosing to the youngest, lowest weight patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

Final Report Submission: December 31, 2010

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

/s/

Elizabeth A Ford
4/30/2009 12:36:15 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 11, 2009
From: Cristi L. Stark, CDER/ODEIII/DGP
To: NDA 20-725 file
Solvay Pharmaceuticals, Inc.
Creon (pancrelipase) Delayed-Release Capsules
Subject: Internal Meeting

PARTICIPANTS:

CDER: Cristi Stark, Anne Pariser, Donna Griebel, Ethan Hausman, Elizabeth Ford, Julie Beitz, Maria Walsh

CYSTIC FIBROSIS FOUNDATION: Preston Campbell III, MD, executive Vice President of Medical Affairs

This meeting was held to discuss vitamin supplementation and monitoring vitamin levels in Cystic Fibrosis patients. Dr. Campbell stated that there is a standard of care for multivitamin supplementation in Cystic Fibrosis patients and agreed to send the documents detailing this to FDA. These documents include information on fat soluble vitamin levels and how often they should be monitored in patients. Dr. Campbell added that at a minimum, patients are checked yearly for vitamin levels. If there is an issue, the monitoring is increased. In addition, infants starting a pancrelipase product usually have blood levels measured two months after the start of medication and then yearly monitoring (or more frequent monitoring if an issue).

FDA inquired if physicians are aware that mineral oil causes a change in vitamin absorption. Dr. Campbell replied that every cystic fibrosis physician is aware that fat malabsorption = fat and vitamin loss. They also understand that if a patient is on a fat/oil that is not absorbed, a change in diet and vitamins is required. If a physician had a patient that changed their pancrelipase treatment which led to a change in bowel levels, they would immediately start measurement of vitamin levels. Dr. Campbell added that this is normal routine with non-branded pancrelipase products or new formulations.

FDA inquired if patients can overdose on vitamins when consuming less mineral oil. Dr. Campbell responded that it is highly unlikely.

The call ended.

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

/s/

Cristi Stark
4/29/2009 11:59:11 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 31, 2009
From: Cristi L. Stark, CDER/ODEIII/DGP
To: NDA 20-725 file
Solvay Pharmaceuticals, Inc.
Creon (pancrelipase) Delayed-Release Capsules
Subject: Internal Meeting

PARTICIPANTS:

CDER: Cristi Stark, Anne Pariser, Donna Griebel, Ethan Hausman, Elizabeth Ford

CYSTIC FIBROSIS FOUNDATION: Preston Campbell III, MD, executive Vice President of Medical Affairs

This meeting was held to discuss how to administer medication to children under the age of one. Dr. Campbell stated that he has seen children with cystic fibrosis receive pancrelipase in the following manner:

- In addition with food (e.g., a small bit of applesauce with the microspheres on top)
 - Two of the main issues with this method include:
 - Sores in the mouth from microspheres retained between the gums
 - Diaper sores/rash from microspheres that are excreted in the diaper undissolved.
- Sprinkle on tongue and blow in face (this method provides a reproducible reflex so the child swallows)

FDA inquired if Dr. Campbell was aware of parents mixing pancrelipase with formula to provide to daycare providers well in advance of consumption. Dr. Campbell replied that this should not happen. The formula will dissolve the enteric coating which leaves the lipase open to be deactivated as soon as it hits the child's stomach. Dr. Campbell added that most parents are aware of how to dose their children and do not do this.

In addition, Dr. Campbell stated that there is a period when children get teeth and still cannot swallow. He stated that children should not crunch the pancrelipase microspheres as this would also break the enteric coating and allow for the enzymes to be deactivated in the stomach.

The call ended.

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

/s/

Cristi Stark

4/29/2009 11:14:17 AM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 20-725 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Creon Established/Proper Name: Pancrelipase Dosage Form: Delayed-Release Capsules		Applicant: Solvay Pharmaceuticals Agent for Applicant (if applicable):
RPM: Cristi Stark		Division: Gastroenterology Products
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input checked="" type="checkbox"/> If no listed drug, check here and explain: based on literature</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 3/9/09</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		3/20/09 (4/30/2009)
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input type="checkbox"/> None AE – 8/17/07, NA – 10/9/03
❖ Promotional Materials (accelerated approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Application ² Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 7 <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	11/12/08
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other HHS Info Advisory

All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10- year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

<p>❖ Copy of this Action Package Checklist³</p>	
<p align="center">Officer/Employee List</p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p align="center">Action Letters</p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) AP- 4/30/09, AE – 8/16/07, NA – 10/9/03</p>
<p align="center">Labeling</p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>3/6/09</p>
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	<p>N/A</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>6/19/08</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>N/A – this will be the first approval after the FR Notice</p>
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None</p>

³ Fill in blanks with dates of reviews, letters, etc.
Version: 9/5/08

<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	See attached to PI
<ul style="list-style-type: none"> Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	N/A
<ul style="list-style-type: none"> Original applicant-proposed labeling 	See attached to applicant PI (it was originally proposed as a PPI)
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	To be submitted soon
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP 2/23/09, 7/23/07, 6/27/07, 4/17/07, 4/9/07, 10/10/03 <input checked="" type="checkbox"/> DRISK 3/9/09, 4/27/07 <input checked="" type="checkbox"/> DDMAC 11/24/08, 4/9/07, 10/10/03, 7/29/03 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> 4/3/09 OBP carton/container review
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> Review(s) (<i>indicate date(s)</i>) Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	See above DMEPA reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	9/24/97, 8/21/97
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html 	
<ul style="list-style-type: none"> Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Postmarketing Requirement (PMR) Studies 	<input type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing communications (<i>if located elsewhere in package, state where located</i>) 	3/6/09, 3/5/09
<ul style="list-style-type: none"> Incoming submissions/communications 	3/6/09
<ul style="list-style-type: none"> ❖ Postmarketing Commitment (PMC) Studies 	<input type="checkbox"/> None

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 9/5/08

<ul style="list-style-type: none"> Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) 	See PMR section where combined, 3/5/09
<ul style="list-style-type: none"> Incoming submission documenting commitment 	See PMR section where combined, 3/6/09, 3/5/09
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>) 	4/30/09, 4/6/09, 4/8/09, 3/31/09, 2/23/09, 2/19/09, 12/18/08, 12/11/08, 12/11/08, 12/11/08, 11/28/08, 11/24/08, 8/15/08, 8/15/08, 7/15/08, 3/17/08, 3/11/08, 1/30/08, 8/16/07, 6/26/07, 5/10/07, 5/8/07, 4/24/07, 4/9/07, 4/3/07, 3/30/07, 3/5/07, 12/4/06, 12/3/03, 11/16/03, 9/22/03, 9/15/03, 7/30/03, 7/2/03, 6/30/03, 6/6/03, 6/2/03, 5/31/03, 11/21/02, 10/23/02, 10/9/97, 8/5/97
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. 	4/24/09, 3/31/09, 3/11/09, 10/1/03, 7/30/03, 5/13/03
<ul style="list-style-type: none"> ❖ Minutes of Meetings <ul style="list-style-type: none"> • PeRC (<i>indicate date; approvals only</i>) • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) • Regulatory Briefing (<i>indicate date</i>) • Pre-NDA/BLA meeting (<i>indicate date</i>) • EOP2 meeting (<i>indicate date</i>) • Other (e.g., EOP2a, CMC pilot programs) 	<input type="checkbox"/> Not applicable 11/12/08 <input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> No mtg 6/14/94 <input checked="" type="checkbox"/> No mtg 11/17/05, 12/16/04, 7/1/03, 6/24/03, 5/28/03
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) • 48-hour alert or minutes, if available 	<input type="checkbox"/> No AC meeting 12/2/08 Full transcripts and quick minutes
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 4/30/09, 8/16/07, 10/9/03
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 4/30/09, 8/1/07, 10/2/03
Clinical Information⁵	
<ul style="list-style-type: none"> ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) ❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>) ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not 	See CDTL reviews, 10/9/03 4/30/09, 8/16/07, 6/22/07, 9/30/03 <input checked="" type="checkbox"/> None Incorporated in clinical reviews Incorporated in clinical reviews

⁵ Filing reviews should be filed with the discipline reviews.
Version: 9/5/08

Clinical reviews from other clinical areas/divisions/Centers (indicate date of each review)	<input checked="" type="checkbox"/> None
Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> Review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) REMS Memo (indicate date) REMS Document and Supporting Statement (indicate date(s) of submission(s)) 	<input type="checkbox"/> None 3/9/09, 2/24/09, 1/30/09 Still in draft
❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested 1/12/09, 12/3/08, 8/26/03, 9/10/03
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None see concurrence on stat reviews
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 11/14/08, 7/17/07, 9/23/03
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 11/10/08, 8/7/07, 8/1/07, 7/16/07, 9/24/03
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None 6/8/07
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None 2/23/09, 8/10/07
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 11/18/08, 8/13/07, 6/25/07, 9/4/03
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 4/28/09, 3/6/09, 8/17/07, 7/30/07, 8/19/03

<ul style="list-style-type: none"> • BLAs only: Facility information review(s) <i>(indicate dates)</i> 	<input type="checkbox"/> None
Microbiology Reviews <ul style="list-style-type: none"> • NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i> • BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i> 	5/4/07 <input type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	8/19/03
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

505(b)(2) ASSESSMENT

Application Information		
NDA # 20725	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Creon Established/Proper Name: Pancrelipase Delayed-Release Capsules Dosage Form: Capsules Strengths: 6000/19000/30000, 12000/38000/60000, 24000/76000/120000		
Applicant: Solvay Pharmaceuticals		
Date of Receipt: June 20, 2008 (complete #3 response received)		
PDUFA Goal Date: March 20, 2009		Action Goal Date (if different):
Proposed Indication(s): treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions		

GENERAL INFORMATION

1. Is this application for a drug that is an "old" antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "YES," proceed to question #3.

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published literature for excipients (journal articles, reference in FR Notice to do this)	Pharmacology/toxicology (labeling informed, safety informed – this is needed to approve from a pharm/tox perspective)

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

N/A

RELIANCE ON PUBLISHED LITERATURE

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #6.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #6

If “YES”, list the listed drug(s) identified by name and answer question #5(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #11.

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

YES NO

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

9. Were any of the listed drug(s) relied upon for this application:

- a. Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b. Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c. Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d.1.
If "NO", proceed to question #10.

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO," to (a) proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "YES" and there are no additional pharmaceutical equivalents listed, proceed to question #13.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #13.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #13.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): N/A

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

15. Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

- No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
- Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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

/s/

Cristi Stark
4/27/2009 12:06:03 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-725

Solvay Pharmaceuticals
Attention: Donald A. Ruggirello
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your June 19, 2008, new drug application (NDA) "Complete Response to Approvable Letter" submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon® (pancrelipase) Delayed-Release Capsules 6000, 12000, and 24000.

On December 8, 2008, we received your December 5, 2008, major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is March 20, 2009.

If you have any questions, call me at (301)796-1007.

Sincerely,

{See appended electronic signature page}

Cristi Stark, M.S.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Cristi Stark
12/11/2008 01:35:18 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-725

INFORMATION REQUEST LETTER

Solvay Pharmaceuticals
Attention: Donald A. Ruggirello
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your June 20, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon (pancrelipase) Delayed-Release Capsules 6, 12, and 24.

We are reviewing the Clinical, Statistical, and Biopharmaceutical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Multiple reviewers cannot access Appendix 12. Please correct or submit an electronic copy of appendix 12, including an electronically mapped and linked table of contents.
2. In Study S245.3.126, patient 0016-00001 was discontinued due to inadvertent ingestion of dye rather than the randomized treatment. This patient was re-randomized as patient 0016-00003 and completed the study. We are unable to locate a rationale for explaining why this error necessitated removal and why re-randomization was performed. Please direct us to the location of this information in your submission. If this information is not contained in the submission please submit an explanation of why the patient was removed and why re-randomization was allowed.
3. In Study S245.3.126, you state that data quality issues occurred in the two patients from site 23. We are unable to locate a description of these data quality issues in your submission. Please direct us to the location of this information in your submission. If this information is not contained in the submission please submit a complete description of the data quality issues from site 23.
4. We have reviewed your submitted *in vitro* stability study of the content of Creon capsules on food to support the proposed alternative mode of administration. In your study protocol, it was stated,

“Two capsules of the to-be-marketed formulation (corresponding to approximately 24,000 USP units of lipase) were opened and transferred into a bag of polypropylene cloth. The bag was put into the food so that the pellets were very well.... After 1 hour incubation at 25°C the bag containing the pellets was removed. Residues of food were flushed from the pellets and lipase activity of the washed pellets was determined.”

The above study design is not robust enough to produce adequate results to support the claim of an alternative mode of administration. The testing of pellets (Creon capsule content) placed in a bag of polypropylene cloth may not reflect the realistic contact of individual pellets with food. Furthermore, use of only one bag per type of food did not provide statistically meaningful data (i.e., mean \pm standard deviation, SD).

Therefore, we recommend the following:

- a. Ideally, pellets (the content of Creon capsules) to be studied should represent the recommended dose of lipase for pediatric population. Before mixing pellets with food in a beaker, the pellets and each type

of acidic food (pH <5.0) should be carefully weighed individually. For each type of food, 8-10 beakers of such mixture should be prepared per test.

- b. Incubation should be performed at 25°C for 1 hour. The pellet/food mixture from four to five beakers should be individually collected after 30 min of incubation. For the rest of the four to five beakers, the mixture should be collected similarly after 60 min of incubation. Food in the collected mixture should be washed off using acidic solution (e.g., pH 1.0) to obtain pellets for further testing.
- c. Thereafter, all the pellets collected from each beaker at each time point should be incubated in an acidic medium (under acidic stage) for two hours, then transferred to, and further tested in, an alkali buffer solution for another 60 min per dissolution methodology specified for the determination of the lipase activities in the pellets. However, if you feel the 2-hr incubation at the acidic stage is not needed, please provide your justification.
- d. Analyze first the lipase activity (% of labeled amount/activity) in the 60-min samples (n=4-5 beakers) for each type of food. If the recovery is lower than your proposed specifications, the lipase activity in the 30-min samples (n=4-5 beakers) should be analyzed further.
- e. The results (mean ± SD) of lipase activities from four to five beakers for each type of food at each time point (30 or 60 min) should be organized in a table.

Finally, revise your proposed labeling to reflect the above study results.

5. Please provide your manufacturing campaign for your drug substance during the times of September through October 2008 for your drug substance manufactured in the Neustadt facility.

If you have any questions, call Cristi Stark, Regulatory Project Manager, at (301)796-1007.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Brian Strongin
8/15/2008 03:39:35 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-725

Solvay Pharmaceuticals
Attention: Donald A. Ruggirello
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Creon.

We also refer to the meeting between representatives of your firm and the FDA on January 17, 2008. The purpose of the meeting was to discuss proposed plans addressing issues identified in the Approvable Letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 17, 2008
TIME: 8:30 AM – 10:00 AM
LOCATION: White Oak
APPLICATION: NDA 20-725
DRUG NAME: Creon
TYPE OF MEETING: Type C
MEETING CHAIR: Anne Pariser, M.D.
MEETING RECORDER: Maureen Dewey, M.P.H.

FDA ATTENDEES:

Division of Gastroenterology Products (DGP)

Anne Pariser, M.D., Medical Team Leader
Ethan Hausman, M.D., Medical Officer
Maureen Dewey, M.P.H., Regulatory Project Manager

Office of Biotechnology Products (OBP), Division of Therapeutic Proteins

Barry Cherney, Ph.D., Deputy Director
Gibbes Johnson, Ph.D., Supervisory Research Chemist
Ennan Guan, Ph.D., Chemistry Reviewer
Howard Anderson, Ph.D., Chemistry Reviewer

Division of Clinical Pharmacology

Tien-Mien Chen, Ph.D., Clinical Pharmacology Reviewer

Office of New Drugs

Sally Loewke, M.D., Associate Director of Policy

EXTERNAL CONSTITUENT ATTENDEES:

Solvay Pharmaceuticals, Inc.

Ron Robison, M.D., M.S., Senior Vice President, Global Regulatory Affairs
Victor Raczowski, M.D., M.S., Vice President, U.S. Regulatory Affairs
Don Ruggirello, Sr. Director, Regulatory Affairs
Gregg A. Pratt, Ph.D., Manager, Regulatory Affairs
Walt Braband, Assistant Director, Regulatory Affairs
Steve Caras, M.D., Director, Gastroenterology, Global Clinical Development

Solvay Pharmaceuticals GmbH, Germany

Hans-Friedrich Koch, Ph.D., Global Project Management, Enzymes
Kristin Forssmann, M.D., Ph.D., Head Therapeutic Area, Enzymes
Jens Onken, Ph.D., Chemical and Pharmaceutical Project Leader
Frauke Ruffer, Ph.D., Head of Biological Safety

Andreas Körner, Ph.D., Head of Enzyme External Development
Katrin Beckmann, Project Statistician

BACKGROUND:

Solvay requested a Type C Meeting to obtain FDA input and concurrence on Solvay's proposed plans for addressing the deficiencies identified in the Approvable Letter for Creon (dated August 16, 2007).

QUESTIONS

General

1. To facilitate timely completion of the application review, Solvay would like to submit responses to CMC and viral safety issues identified in the Approvable Letter prior to the submission of the clinical data. This information would be submitted as the information becomes available. Will the Agency agree to review responses and provide feedback prior to a complete response to the Approvable Letter (Attachment 1) in a rolling submission concept?

Response:

No. In order for your response to the Approvable letter to be considered a Complete Response, you must respond to all deficiencies delineated in the letter. We will not consider your submission as a Complete Response and the regulatory review clock will not start until all of the necessary information has been received, and an assessment has been made by the Agency that the submission constitutes a Complete Response. We cannot provide feedback until we have been given the opportunity to review your Complete Response.

Additional Discussion:

FDA will continue to provide ongoing communication to the extent possible. All requests should be submitted to the RPM.

Clinical

To respond to the clinical issue in the Approvable Letter, Solvay is conducting two studies, one in pancreatitis and pancreatectomized patients (S245.3.124), and the other in cystic fibrosis patients (S245.3.126) to evaluate the safety and efficacy of the Creon to-be-marketed formulation. Solvay recently received comments from FDA on both study protocols, and affected changes to the protocols resulting from the comments received. For your convenience, the Synopses for studies S245.3.124 and S245.3.126 are provided as Attachments 2 and 3, respectively. In addition, Solvay will provide a status report on the enrollment in these studies to the Agency in advance of the meeting.

In this meeting, we would like to seek clarification on issues relating to the evaluation of efficacy in these trials, in particular as they relate to disease severity and sub-group

analyses. In addition, we seek agreement on the format and content of the Integrated Summary of Safety and supporting tables for labeling.

Questions relating to study S245.3.124 in patients with Chronic Pancreatitis (CP)

2. It has been suggested in our interactions with FDA (Agency comments on the study protocol dated 21 May 2007, and our 21 August 2007 teleconference) that demonstration of a 30% change in CFA in severely affected patients will be one criterion for approval. To demonstrate this, we will perform a sub-group analysis comparing intra-individual changes in CFA from baseline to the end of the randomized period in severe CP patients (CFA at baseline $\leq 50\%$). In this sub-group, we intend to demonstrate in patients randomized to Creon that the mean intra-individual change in CFA is greater than or equal to 30%. We will not compare results to placebo since the study is not powered for this analysis. Does the Agency agree with this approach?

Response:

We do not object to your performance of a sub-group analysis comparing intra-individual changes in coefficient of fat absorption (CFA) from baseline to the end of the randomized period in severely affected patients without a direct comparison of the results between the two treatment groups, as you have stated in the meeting briefing package. However, we will be basing our determination of the efficacy of your product on a complete review of the clinical data you submit in your Complete Response. This assessment will include a thorough review of the results submitted for the individual study(ies), such as analyses of the pre-specified primary endpoint(s) and other endpoints, subgroup analyses as appropriate (e.g., by baseline CFA), and review of individual patient data, among others.

Additional Discussion:

FDA clarified that performance of a subgroup analysis as delineated above is appropriate; however, the totality of the data, including prespecified primary and other endpoints in addition to other subgroup analyses, will be used as evidence of efficacy. Efficacy determination will be made upon review of the entire Complete Response submission.

3. As stated in Question 2, to satisfy the proposed efficacy criteria in the CP study (S245.3.124), we intend to define "severely affected" as baseline CFA $\leq 50\%$. Does the Agency agree with this definition?

Response:

For exocrine pancreatic insufficiency "severely affected" is generally defined in the medical literature as a baseline CFA $\leq 40\%$, and this is the cut-point we will use in our sub-group analyses for severely affected patients.

Questions relating to studies S245.3.124 and S245.3.126

4. Both studies (S245.3.124 and S245.3.126) are planned to enroll US-based patients, as well as patients from non-US sites, for example Israel, Poland, Bulgaria, Hungary, Russia, and South Africa. All efforts are being made to provide for consistent diagnostic criteria in accordance with those used in the US and to standardize fat consumption across all participating sites. Does the Agency require a minimum percentage of patients originating from the US?

Response:

No. There is no minimum number of US patients that must be enrolled in an IND study. Please note, however, that all studies that will be used to demonstrate the efficacy and safety of your product must be conducted in accordance with Good Clinical Practice (GCP) standards, and all data must be available for inspection by the Agency, if necessary.

Questions relating to the complete clinical response:

5. Solvay currently has two ongoing clinical studies (CP, S245.3.124, and CF, S245.3.126) to evaluate the safety and efficacy of the to-be-marketed formulation. In our complete response we intend to submit the data from the first study to finish. It is our understanding that data from this one study, if compelling, together with the totality of other information contained in the NDA, will be adequate to support approval of CREON for the treatment of PEI in both CF and CP/pancreatectomized patients. Does the Agency agree?

Response:

Yes; however, if you are relying on a single study, the study must clearly demonstrate substantial evidence of clinical benefit.

Additional Discussion:

FDA clarified that study designs for the above studies have previously been commented on. Please see the Agency's previous responses. Should Creon be approved, the indication would likely be for the treatment of steatorrhea in PEI, and not by individual cause of PEI by underlying disease.

6. Efficacy data from the study that we submit will be provided in the clinical study report. We do not intend to submit an updated section 8.7 (ISE) of the NDA. Does the Agency agree with this approach?

Response:

Yes. You are only required to respond to the deficiencies stated in the Approvable letter. Please note that the content and format of the clinical study results submitted to us must conform to the requirements as stated in 21 CFR 314.50 (e.g., submission contains tabulations of the data, and these data are reviewable). If there is additional information related to the effectiveness of

your drug that is available at time of submission of the Complete Response, please also include this information in the submission.

7. As requested by the Agency in our 16 August 2007 Approvable Letter, the format for the Integrated Safety Summary (ISS) will be the same as used for the November 2006 submission (Attachment 4). The Creon NDA Safety Update 2006 will form the baseline for the ISS. Newly integrated data will be limited to new data resulting from one efficacy study (S245.3.124 or S245.3.126), the three Japanese studies (K245.5.703, S245.3.103, and S245.3.104) for which datasets have been submitted but were not integrated in the November 2006 update, and one additional Japanese study (S245.2.002) for which the dataset has not yet been submitted (though the final clinical study report has been submitted). In addition, we will submit SAE's from any ongoing studies. Does the Agency find this approach acceptable?

Response:

Your approach appears to be reasonable. In order to facilitate our review of the new data as well as the overall integrated safety results, please clearly identify and describe the studies included in the ISS, the specific formulations used in each study, patient exposure, and populations studied, among other requirements for an ISS (as stated in 21 CFR 314.50). In addition, the accompanying datasets must be amenable to review and manipulation, so that the new information (i.e., information not previously available for review in the previous submission) is able to be extracted and independently reviewed, or appears separately by individual study.

Additional Discussion:

FDA clarified that the content of the previous ISS was not problematic, but some of the datasets (as delineated in the above response) were difficult to work with. The most important data to be submitted will be the safety data from ongoing and completed studies with the intended to-be-marketed product that have not previously been reviewed. FDA reiterated that the ISS dataset should allow for separation by study and formulation in addition to other required fields.

In addition to the submission of SAEs from ongoing studies (as noted above), at the time of submission of the Complete Response, please submit interim safety reports from your ongoing studies that will provide us with current safety information (all safety information from ongoing studies to within a three-month cut-off of your submission of the Complete Response).

Additional Discussion:

FDA reiterated that we will require an interim safety summary from all ongoing studies for all safety information to within a 3 month cut-off of submission of your Complete Response. Otherwise, a safety knowledge gap would exist.

8. Is the structure of the data presentation of adverse drug reactions in the proposed labeling submitted in the November 2006 submission (and subsequently updated during the NDA review) acceptable to the Agency? We ask this question to assure that we will generate all required tables in the updated ISS to support labeling. The proposed labeling is provided in Attachment 5.

Response:

Probably not. The most meaningful adverse reaction (AR) data that should appear in product labeling will be from randomized, double-blind, placebo-controlled studies with your intended-to-be-marketed product (TbMP). Pooling of the data should only occur if the studies used comparable products, and had similar study designs and study populations, which does not appear to be the case with the tables you have included in draft labeling. If the AR profiles from different populations treated with your TbMP are substantially different, it may be necessary to describe these AR profiles separately. Similarly, the AR profile from different populations treated with previously marketed formulations and currently marketed formulations should be presented separately. Should your application be adequate for approval, the specific wording and content of the labeling will be negotiated during the review cycle after a complete review of the submission has occurred.

At this time, we are more concerned about the content and format of the tabulations of the clinical data (datasets) that will be submitted in support of the ISS, particularly for the ongoing studies (S245.3.124, and S245.3.126) that are intended to demonstrate the efficacy and safety of your TbMP product. To facilitate review, your electronic datasets should clearly identify study name, formulation used, unique patient identifier, dose, duration of exposure, date of onset of any AR, onset of AR in relation to treatment [TbMP or placebo], duration of AR, assessment of relatedness of the AR to treatment and seriousness of the AR, among other information. From the prior submission, the format of the electronic datasets for the following two studies was adequate for clinical review:

S248.3.003: "Open-label, Single-arm, Multicenter Study to Evaluate the Efficacy and Tolerability of Creon[®] for Children in Infants with Pancreatic Exocrine Insufficiency Caused by Cystic Fibrosis (S248.3.003)"

S245.3.115: "A Double-blind, Multi-center, Randomized, Parallel Group Comparative Study to Prove Superior Efficacy of SA-001 versus Placebo in Patients with Pancreatic Exocrine Insufficiency Caused by Chronic Pancreatitis or Pancreatectomy (S245.3.115)"

Prior review of your ISS in the previous submission revealed problems with some of the datasets and study information. For example, apparent differences in the number of patients who experienced ARs in different adverse event/adverse reaction datasets and the seriousness of ARs in different datasets where multiple events were

not classified regarding seriousness were seen. In addition, please clearly distinguish tabulation datasets (i.e., listing datasets) from analysis datasets.

Additional Clinical Questions

9. On 31 July 2007 Solvay submitted a document containing additional analyses related to our S245.2.003 cross-over pharmacology study (Attachment 6). These analyses were conducted to address Agency concerns expressed in our 26 April 2007 teleconference regarding the variability of enzyme release observed in this intubation study. Would the Agency provide comment on these analyses, and on the viability of the study results in light of the additional analyses?

Response:

1. **The comparability between the to-be-marketed and clinically tested formulations could not be demonstrated.**
 2. **The variability of pancreatic lipase recovery between patients was very high. The primary cause of the variability was the subjects' endogenous lipase secretions.**
 3. **Patients with chronic pancreatic insufficiency should be screened more thoroughly for baseline endogenous lipase levels prior to being enrolled into the study.**
10. Are there any additional points that the Agency would like to advise us on to ensure that we have a complete submission that will be approved?

Response:

A determination as to the adequacy of the submission to support approval will be made during the review cycle after receipt and review of the submission.

We have the following additional comments:

- **The pediatric studies included in the previous submission were performed using a different Creon formulation that has not been demonstrated to be comparable to the TbMP. One of your ongoing studies (S245.3.126) proposes to include patients with Cystic Fibrosis as young as 12 years of age. Since Creon will almost certainly continue to be used by pediatric patients as young as one month of age, should the product be approved, you need to propose a pediatric plan for the evaluation of safety and efficacy of the TbMP in younger patients (ages one month to <12 years). Please note that your product can only be labeled for the populations included in the clinical development program, for which there is acceptable evidence of safety and efficacy.**
- **A formulation of Creon suitable for administration to pediatric patients unable to swallow capsules will need to be developed in accordance with PREA regulations. We are concerned "that opening capsules and sprinkling pellets" and estimating the dose may pose some risk of lipase overexposure to the youngest patients and**

increase the risk of fibrosing colonopathy in the patients most at risk of experiencing this complication. For example, for a one month old, who weighs 5 kg, the recommended starting dose of 500 units of lipase/kg/meal would be 2,500 units of lipase per meal. The smallest capsule dose is 6,000 units, thus, accurately measuring the 2,500 unit dose of Creon would be difficult, particularly, if parents were to follow the diagrams provided in the Patient Information section of the proposed labeling. Please clarify how you intend to address this issue.

Additional Discussion:

FDA stated that since we were unable to link the currently marketed product with the intended to be marketed product, previously submitted pediatric data cannot be used as primary evidence of efficacy and safety in younger patients. We recommend that Solvay submit a pediatric plan for the evaluation of younger patients, and for the development of an age-appropriate formulation as soon as possible. Solvay stated that a pediatric plan is in progress, which will be submitted, and can be the subject of future discussion.

CMC

Items from the Approval letter are provided below, followed by Solvay's position for discussion and response.

11. **Due to the critical role of (b) (4) in lipase activity, adequate control of (b) (4) activity must be ensured in the drug substance and drug product. We recommend that the measurement of lipase potency in release and stability testing be performed in both the absence and presence of excess exogenous (b) (4). Acceptance criteria for activity under each assay condition should be established and justified.**

Solvay's Response: Based on the lipase activity results of the drug substance and drug product both in the absence and presence of excess exogenous (b) (4), Solvay's Creon product contains enough (b) (4) and is not affected by excess exogenous (b) (4). Solvay has tested additional drug substance and drug product on initial release and aged samples (Attachment 7). These data confirm Solvay's drug substance and drug product contain sufficient (b) (4) and the lipase acceptance criteria in both the absence and presence of excess exogenous (b) (4) would be the same. Therefore, an additional specification and testing are not required. Does the FDA agree?

Response:

We agree that after a review of the summary information provided there is not likely to be additional value in performing the drug substance and product lipase testing in the absence and presence of exogenous (b) (4). However, more information is required to make a final determination, and more data are required to demonstrate that all drug substance lots manufactured will have consistent levels of (b) (4). Please provide the following:



Additional Discussion:

Solvay Slide #11:

Solvay will submit the requested information as a submission to the NDA.

With respect to (iv), the Agency stated that it will be acceptable to assign the masses of the various components within the peaks in the preparation. Solvay should demonstrate that the (b) (4) is consistent in their manufacturing lots to avoid routine monitoring. Solvay should submit the information on the qualification of the (b) (4) assay.

12. Perform dissolution testing of the drug product on intact capsules.

Solvay's Response: As discussed and agreed to with the FDA in our October 2005 meeting, the dissolution of the Creon product is similar with or without the capsule shell. The dissolution briefing document as well as FDA's meeting minutes are included in Attachment 8. Additional comparative dissolution data to support this position is also presented in Attachment 8. Therefore, Solvay proposes to continue to perform the dissolution of the drug product on the pellets instead of the intact capsules. Does the FDA agree?

Response:

Yes.

Viral Safety

Items from the Approval letter are provided below, followed by Solvay's position for discussion and response.

13. In order to conclude that the manufacturing process provides adequate capacity to inactivate enveloped viruses, the input viral loads must be known. Provide information on potential enveloped viral loads, and provide an overall assessment on the ability of the process to effectively control this level of viral load.

Solvay's Response: Based on considerations that:

- a. Solvay has instituted numerous selection criteria, approval procedures and controls for the sourcing and handling of the raw material ensuring that pancreas glands are exclusively derived from pigs certified as fit for human consumption thus minimizing the introduction of enveloped viruses into the process (See Attachment 9- Section 1),
- b. Viral Clearance Studies have been performed to determine the total logarithmic inactivation factors (LRF), (b) (4)
(b) (4)
 - (b) (4) for Bovine Viral Diarrhea Virus,
 - (b) (4) for Pseudorabies Virus,
 - and (b) (4) for Xenotropic Murine Leukemia Virus;

During the studies, instantaneous and complete inactivation of enveloped viruses (b) (4) in the load sample was observed.

Furthermore, a demonstration of larger LRFs was limited by increased detection limits of the cell-culture based assays due to unique cytotoxic effects of Pancrelipase on detector cells, (See Attachment 9- Section 2).

- c. An assessment on the probability and significance for the presence of porcine enveloped viruses in the raw material under consideration of etiology, prevalence, surveillance measures, way of transmission, zoonotic potential, and organ tropism has been performed, (See Attachment 9- Section 3).

Solvay proposes to determine the initial enveloped virus load by investigation of 50 batches of starting material for the presence of two representative, relevant enveloped viruses, *Porcine cytomegalovirus* and *Transmissible gastroenteritis virus*. Both viruses represent two of the most common and widely distributed enveloped viruses in swine, and are therefore applicable to model the worst case contamination of the raw material with enveloped viruses in order to assess the ability of the process to effectively control this level of viral load. It is proposed to employ Q-PCR technique since this represents the most sensitive and efficient way to detect and quantify viral genomes.

Solvay requests feedback from the Agency on whether the described approach is acceptable to provide information on potential enveloped viral loads and if Solvay can complete this testing as a post approval commitment. Does the Agency agree with this approach?

Response:

We agree with your proposed approach to detect and quantify enveloped viral load by employing Q-PCR with 50 batches of starting material for presence of CMV and TGV genomics. However, we have two comments.

- 1. Your evaluation should include enveloped viruses that have a zoonotic**

potential and are at risk to be present in the source material. It is unclear why you believe the two viruses chosen are representative of the potential viral loads for other viruses. We believe both vesicular stomatitis virus and swine influenza virus A should be included in your evaluation. Please provide information on why the chosen viruses are representative of potential viral loads or include the additional viruses in your assessment.

Additional Discussion:

Solvay performed a risk assessment, and concluded that there was little risk that these viruses would be present in the product due to their tissue specificity (i.e., the pancreas is not the target tissue) and lack of cross contamination during the tissue procurement procedure. FDA agreed that this approach could be acceptable if supported by the scientific literature and manufacturing process. Solvay will submit the rational and reference information that supports this conclusion.

2. While it is acceptable to complete your evaluation of multiple batches of starting materials as a post approval commitment, please submit to the application sufficient information regarding a general assessment of these viral loads prior to approval. Please include your rational for the specific data sets provided.

Additional Discussion:

See Slide #13 Response regarding whether a qualitative risk assessment would be regarded as sufficient information.

FDA emphasized that Solvay should provide sufficient quantitative information concerning the viral loads for review prior to approval. Solvay agreed to conduct an analysis on an appropriate number of lots for an initial assessment of viral loads prior to approval, and to submit the rationale for the size of the data set.

14. Viral testing indicates that your drug substance contains infectious parvovirus (PPV), and the evaluation of your manufacturing process indicates that it has limited capacity to remove PPV. While you have not detected infectious PPV in the small number of drug product lots examined, there are insufficient data to indicate that infectious particles can be adequately controlled by the manufacturing process. Establish specifications for the presence of infectious PPV, or provide compelling evidence that the manufacturing process is capable of controlling the level of PPV in the final product.

[...]

Solvay requests feedback from the Agency on whether the described approach is acceptable. Further, Solvay requests whether the Agency agrees on the specifications set for PPV DNA and infectivity.

Response:

No, we do not agree with your proposed approach and have the following comments:



Additional Discussion:

Solvay Slide #14(1):

Based on this clarification, does the Agency agree on the proposed specification of (b) (4) copies/gram of drug substance given that Q-PCR Assay I is used for batch release testing?

FDA Response:

No, we do not have sufficient information to reach a definitive conclusion. If you wish to establish specifications/action limits for the copies/gram of drug substance based on the results from the Q-PCR assay I, then you must provide the data that link the Assay I results to infectivity. FDA recommended that Solvay change the specification for copies/gram to an action limit, and report the results on the COA.

Solvay Slide #14 (2):

Considering the modified specification, does the Agency agree with Solvay's approach?

FDA Response:

No, we do not have sufficient information to reach a definitive conclusion that this specification is acceptable. You must submit for review all data that were used to establish the specification for the limits on infectious PPV. You should include information on assay performance for the additional infectivity assay that was used. Solvay should also provide information confirming that these lots are representatives of the commercial process.

Solvay inquired if their proposal for HEV virus is acceptable. The Agency stated we cannot answer the question without information demonstrating how PPV can serve as an indicator for HEV infectivity. Solvay should submit the information to the NDA.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-725

ADVICE LETTER

Solvay Pharmaceuticals
Attention: Donald A. Ruggirello
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your November 17, 2006, new drug application (NDA) "Complete Response to Not Approvable Letter" submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon[®] (pancrelipase) Delayed-Release Capsules 6, 12, and 24.

We have reviewed your submission, and have the following comments and recommendations. Although these are not approvability issues, response to them is requested.

Microbiology

(b) (4) testing is a change in product specifications and would require the submission of a prior approval supplement to the application. The supplement should include sufficient data and justification to support (b) (4) testing regarding microbial limits.

Clinical and Statistical

The unplanned interim analysis for adjustment of sample size that was performed in Study S245.3.115 (adult exocrine pancreatic insufficiency study conducted in Japan) resulted in the reported p-values for the final analysis not being interpretable, and no formal statistical adjustment could be applied.

For your two Phase 3 studies conducted under protocols S245.3.124 (chronic pancreatitis) and S245.3.126 (cystic fibrosis), there are currently no interim analyses planned. If you do plan to modify the protocols and conduct an interim analysis, you will need to submit a complete interim analysis plan to the Division for review and comment prior to conduct of the interim look. The plan should specify the purpose of the interim look (e.g., sample size adjustment or early stopping), alpha-level for the interim look and statistical adjustment to the overall study alpha-level, criteria for action, and what is done if the interim look yields significant results.

Labeling

A. CONTAINER LABEL

1. You use the same blue font color for the “Creon” portion of the proprietary name and for all three product strengths. Although you use differing color strips (b) (4) to differentiate the strengths, this does not provide an adequate difference to minimize the types of selection errors we have encountered with medication errors. In the revised labeling, we note that the color strips for Creon 6,000 and Creon 12,000 are still featured in a (b) (4)-colored font, and there is not sufficient color contrast between Creon 6,000 (b) (4) and Creon 12,000 (b) (4). When comparing the colors side-by-side, it is difficult to distinguish between the different shades. Look-alike labels/labeling with similar color schemes may lead to product selection errors, especially when the products with these similar labels are stored in the same physical location.

All container labels and carton labeling should be revised so that the product strengths within the Creon product line are clearly distinguishable from one another. Each numerical portion of the proprietary name (i.e., 6,000, 12,000, and 24,000) should have a different and distinguishable color from the “Creon” portion of the proprietary name. Additionally, ensure that the color of the vertical strip is the same color as the numerical portion of the proprietary name of the corresponding product strength to increase differentiation.

2. Increase the size of the numerical portion of the proprietary name, so that it is the same size as “Creon”, as this will be used to distinguish these products from one another.
3. Delete or relocate the graphic image above the proprietary name. In its current location it distracts from important information such as the proprietary name and the strength.
4. Ensure the statement “usual dose” is used in conjunction with the statement “See package insert” on the professional sample containers and on the 100 count Creon 6,000, if space permits.
5. Revise the “lift here” statement to read: “Lift here for Active ingredients”, if space permits.
6. Drug product labeling has been proposed as “Store CREON Capsules at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)”. Please specify the length of time for the permitted excursions in temperature.

B. FOIL POUCH LABEL

7. Revise the “lift here” statement to read: “Lift here for Active ingredients”, if space permits. See Container Comments A1 through A4.

8. We note each pouch contains the same (b) (4) color strip. This may also contribute to visual similarity of each pouch leading to selection errors. In revising the color differentiation scheme for the product outlined in comment A1, consider the removal of the (b) (4) strip that appears on all strengths or revise it to match the color chosen in the new scheme so that there are no color overlaps on any pouch.

C. CARTON LABEL

9. See Container A1 through A4.

D. PRODUCT LABELING

10. The following wording regarding pregnancy is to be included in the “USE IN SPECIFIC POPULATIONS; Pregnancy” section of the product labeling:

“8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects

Pregnancy Category C

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

If you have any questions, please call Maureen Dewey, Regulatory Health Project Manager at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff (CPMS)
Safety Regulatory Project Manager (SRPM)
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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Julieann DuBeau
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-725

Solvay Pharmaceuticals, Inc.
Attention: Donald A. Ruggirello
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your November 17, 2006, new drug application (NDA) "Complete Response to Not Approvable Letter" submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon[®] (pancrelipase) Delayed-Release Capsules 6, 12, and 24.

We also refer to your submission dated May 23, 2007, received May 29, 2007 requesting feedback on your product's capsule imprint.

We have completed our review of your capsule imprint and have the following comments and recommendations.

Instead of the proposed imprints of just a portion of the strength, we recommend the use of imprints which are a continuation of the line of imprints utilized for currently marketed Creon products that utilize the company name and NDC #. The drug name is also acceptable in lieu of the company name (e.g., "CREON" and "1206" for Creon 6000, "CREON" and "1212" for Creon 12,000, and "CREON" and "1224" for Creon 24,000). This consistency should help to minimize confusion and potential error among healthcare professionals and patients especially during the time period when all six strengths are marketed. This consistency will help minimize confusion because practitioners are aware of this type of identification scheme.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager at (301) 796-0845.

Sincerely

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
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NDA 20-725

Solvay Pharmaceuticals, Inc.
Attention: Donald A. Ruggirello
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your November 17, 2006, new drug application (NDA) "Complete Response to Not Approvable Letter" submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon[®] (pancrelipase) Delayed-Release Capsules 6, 12, and 24.

We also refer to your submission dated May 11, 2007, received May 14, 2007 containing a new clinical protocol (S245.3.126). The protocol is entitled, "A double-blind, randomized, multi-center, placebo-controlled, cross-over study to assess the efficacy and safety of Creon[®] 24,000 in subjects with pancreatic exocrine insufficiency due to cystic fibrosis."

We have completed our review of your submission, and have the following comments and recommendations.

1. Your inclusion criteria state that patients will be included in the study if they have "an historical Coefficient of Fat Absorption (CFA) <70% without supplementation or current or historical human fecal elastase < 50 µg/stool". State the time frame within which the screening CFA or fecal elastase must have been obtained in order to qualify the patient for entry into the study (e.g., within the last 12 months). Alternatively, incorporate a pre-study non-treatment phase wherein baseline CFA is assessed. Please also correct the elastase reference units to µg/g of stool.
2. The primary efficacy population should be the ITT population, that is, all subjects who were randomized and had taken at least one dose of study medication.
3. Propose how missing data will be accounted for in the analysis.
4. Clearly define the primary endpoint for the study. For example, if you intend to use the mean change of Creon treatment period CFA minus placebo period CFA as the primary endpoint, define this endpoint in your study protocol.
5. Please ensure that your study is adequately powered to demonstrate a clinically meaningful difference in CFA between the Creon and placebo treatment periods. A clinically meaningful change in CFA has been described in the medical literature as a 30% increase in CFA from no-treatment to active treatment in the most severely affected patients (patients with a no-treatment CFA of less than 40%).

6. Based on your responses to items 2, 3, 4, and 5 above, please re-calculate sample size.
7. The doses indicated in sections 2 and 7.6 of your protocol indicate patients would be treated with the higher of either 4,000 lipase units/gram of fat intake per day or 2,500 lipase units/kg/meal. Please specify the dose you intend to study.
8. Clarify what is meant by the effect size of (b) as stated in section 10.8 on page 36 of the protocol.
9. Clearly define all other endpoints (e.g., secondary endpoints) in the study protocol.
10. Your final exclusion criterion states that patients will be excluded for known infection with HIV. Please clarify how HIV infection will be assessed.
11. Since FD&C Blue #2 dye will be administered to all patients as part of study procedures, include information about its adverse reaction profile in both the Investigator's Brochure and the patient Informed Consent form.
12. Section 7.8 (Prior and Concomitant Therapy) of your protocol states that "concomitant medications influencing and (sic) duodenal pH... and drugs acting on gastric emptying... or drugs interfering with bile secretion... can be given in a stable dose throughout the study". Please clarify how "stable dose" will be defined. For example, clarify over what period of time patients will have been taking the medication prior to study entry, state that the dose of the medication has not changed during this time, and state that the medication must be commercially available and be administered in the recommended dose range.
13. The Flowchart of Study Assessments (Table 2) is inadequate. Provide a flowchart that includes all study procedures to be performed by study day rather than grouped by phase as currently depicted in the study flowchart. For example, during Visit 2 Randomization, clearly delineate which protocol-defined treatments and procedures are to occur on each of the four to five days of this period.
14. In Section 8 (Study Assessments and Flow Chart) of the protocol, clearly list and describe in detail, all protocol-related procedures that are to be performed and recorded. For example, clarify on which days vital signs will be obtained and how often.
15. Ensure agreement between the study flowchart and the description of the study procedures in Section 8 (Study Assessments and Flow Chart).
16. No follow-up visit is scheduled after discharge from the inpatient unit at the end of the second cross-over period. Please add a follow-up visit (or telephone call) within several days after discharge for a safety assessment.

17. Define procedures to be used to verify compliance with all study-related procedures, such as compliance with study medications, concomitant medications, and patient self-collections of study endpoints (e.g., diary entries).
18. Your protocol does not state that assent will be obtained from patients ages 12 through 17 years. Per the Code of Federal Regulations (CFR), 21 CFR Part 50, Subpart D 50.52(c), any clinical investigation involving children should document that adequate provisions are made for soliciting the assent of the children. Please describe how you will obtain assent from patients ages 12 through 17 years participating in this study, and submit a copy of the model assent form to be used for our review.
19. Please submit sample Case Report Forms (CRFs), a model informed consent form, and a copy of the investigator's brochure with the revised protocol for our review.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager at (301) 796-0845.

Sincerely

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 47,546
NDA 20-725

Solvay Pharmaceuticals, Inc.
Attention: Donald A. Ruggirello
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon[®] (pancrelipase) Delayed-Release Capsules 6, 12, and 24.

We also refer to your submission dated November 17, 2006, received on November 20, 2006, that included a complete response to our October 9, 2003, Not Approvable Letter.

We further refer to your protocol amendment dated March 8, 2007, received, March 9, 2007 containing a new protocol under IND 47,546. You note that the study will "also provide additional clinical experience using the Creon to-be-marketed product for which Solvay is seeking approval in NDA 20-725."

We also refer to the teleconference between representatives of your firm and the FDA on April 26, 2007. The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any question, please call me at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Dan Shames, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

MEMORANDUM OF TELECON

DATE: April 26, 2007

APPLICATION
NUMBER: NDA 20-725

BETWEEN:
Name:

Don Ruggirello, Senior Director, Regulatory Affairs
Walt Braband, Assistant Director, Regulatory Affairs
David Boyd, Pharm D., Assistant Director, Gastroenterology Clinical
Development
Stephen Caras, Director, Gastroenterology, Clinical Development and
Medical Affairs
Stephen David, Quality Assurance
Fredericke Henniges, Ph.D.,
Hans-Friedrich Koch, Ph.D., Global Clinical Director
Katrin Beckmann, Project Statistician

Representing: Solvay Pharmaceuticals

AND

Name: Julie Beitz, M.D., Director, ODE III
Daniel Shames, M.D., Deputy Director, ODE III
Brian E. Harvey, M.D., Ph.D., Director, Division of Gastroenterology
Products (DGP)
Anne Pariser, M.D., Medical Team Leader, DGP
Ethan Hausman, M.D., Medical Reviewer, DGP
Maureen Dewey, M.P.H., Regulatory Health Project Manager, DGP

SUBJECT: Clinical Study

The Division communicated to Solvay (the Sponsor) that we are concerned about the results of the bioavailability study submitted to the NDA for Creon. Specifically, the bioavailability study had results available for review for only a small number of patients (n=9), and these results were highly variable (e.g., the lipase results post-Creon administration ranged from 0 to 200,000 units). The Division stated that we are unable to bridge the Currently Marketed Product (CMP) and the To-be-Marketed Product (TBMP) with the results obtained in this study. The Division stated that clinical efficacy data will be needed with the TBMP, and we are requesting that Solvay conduct at least one study

with the TBMP in order to demonstrate efficacy. This study should be conducted as soon as possible.

The Sponsor stated that the bioavailability study was designed and conducted per agreement with the Division. The Division stated that it was not the study design that was a problem, but rather the data obtained in the study. The Sponsor also agreed that clinical data are needed with the TBMP, but they proposed conducting the study post-approval. The Division stated that this would not be possible as there is no way to bridge the efficacy demonstrated with the CMP with the TBMP with the bioavailability study. Therefore, a new study with the TBMP is needed.

The Division additionally noted that Solvay had submitted a proposed new protocol for an efficacy and safety study with the TBMP. The proposed study is a two part study: the first part has a randomized, double-blind, placebo-controlled, short-term efficacy design; and the second part has an open-label, uncontrolled, longer-term (approximately six months), safety and secondary efficacy design. The Division will be communicating recommendations to Solvay on the design and conduct of the proposed study in the near future; however, only the first part of the study will be needed to demonstrate efficacy of the TBMP, and it was recommended that the two parts of the study be conducted as separate studies rather than as a combined study.

The Sponsor stated that this study is currently enrolling, and that they expect to complete the study in Quarter 1 of 2008. The Sponsor asked if the current study could be amended at this point to two separate studies. The Division responded yes, so that a complete report of the first study could be submitted as soon as possible.

The Sponsor asked if a single study would support approval. The Division responded that it would depend on the results. Substantial evidence of efficacy will need to be demonstrated with the TBMP. The medical literature defines evidence of clinically meaningful benefit as a 30% increase in the coefficient of fat absorption (CFA) on a 72-hour fecal fat collection in the most severely affected patients (i.e., those with Baseline CFA $\leq 40\%$). The most severely affected patients will need to be represented in this study, and since the Sponsor is proposing that patients be enrolled in the study with Baseline CFA $\leq 80\%$, the Division expects that the patient population would be across the spectrum of disease severity by Baseline CFA. Since patients with more severe disease at Baseline tend to demonstrate larger responses to treatment, the results for the study will depend on the numbers of patients enrolled in each of the Baseline disease severity subgroups. The Division recommended that the Sponsor also consider conducting a study in Cystic Fibrosis (CF) patients.

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/s/

Daniel A. Shames
5/10/2007 06:27:29 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-725

Solvay Pharmaceuticals
Attention: Donald A. Ruggirello
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon[®] (pancrelipase) Delayed-Release Capsules 6, 12, and 24.

We also refer to your submission dated November 17, 2006, received on November 20, 2006, that included a complete response to our October 9, 2003, Not Approvable Letter.

We have reviewed the referenced materials for your proposed trade name and labeling and have the following comments.

Trade name

We do not recommend the use of the proprietary name Creon[®] 6, Creon[®] 12, and Creon[®] 24 for the following reasons:

- 1) Numerical Suffix in the Proprietary Name: We recommend you revise the name to Creon[®] 6,000, Creon[®] 12, 000 and Creon[®] 24, 000 since the lower numbers (6, 12, and 24) could be misinterpreted as the number of tablets to administer. We believe that the use of the numerical suffix 6, 12, and 24 as part of the proprietary names could result in the potential for confusion with the currently marketed products Creon[®] 5, Creon[®] 10, and Creon[®] 20.
- 2) Old and New Formulation Availability: There is the potential for confusion between the old and new formulation if the old Creon[®] formulation is co-marketed with the proposed formulation. We recommend that Creon[®] 5, Creon[®] 10, and Creon[®] 20 be removed from the market once the Creon[®] 6, 12 and 24 is approved.

Labeling

The following issues/deficiencies have been identified in your proposed labeling.

- 3) Revise the name as recommended on all labels and labeling to clearly reflect the lipase component i.e. Creon[®] 6,000, Creon[®] 12,000 and Creon[®] 24,000.
- 4) The font color used for the text on the Creon[®] 6 (b) (4) and Creon[®] 12 (b) (4) is too light and is difficult to read on the contrasting white background. Revise the colors in order to increase readability and provide sufficient color contrast.
- 5) Since the bottles are unit-of-use, please ensure they have child-resistant caps (CRC) to be in compliance with the Poison Prevention Act.

A. FOIL POUCH LABELING PROFESSIONAL SAMPLE

1. The established name appears less than one half the size of the proprietary name. Increase the prominence of the established name so that it is at least one half the size of the proprietary name per 21 CFR 201.10(g)(2).
2. Relocate the statement “KEEP BOTTLE INSIDE FOIL POUCH UNTIL READY TO TAKE” to above the dosage and administration statement to ensure that this important information is not overlooked.
3. Decrease the “UNIT-OF-USE” and “Rx only” statements, as they are as prominent as the trade name, and more prominent than the established name and strength.
4. Ensure the lettering of the foil pouch is readable.

B. CONTAINER LABELING PROFESSIONAL SAMPLE

1. See General Comments A1 and A2.
2. As currently presented, the established name is listed as pancrelipase delayed release capsules. However, information pertaining to the actual amount of lipase, protease and amylase is not presented. Add the strength statement:

Each capsule contains enteric coated spheres of:
Lipase 6,000 USP Units
Free Protease 19,000 USP Units
Amylase 30,000 USP Units

This will provide healthcare providers with the actual amount of these individual components.

C. CARTON LABELING PROFESSIONAL SAMPLE

See General Comments A1 and A2

D. INSERT LABELING

In the General Dosing Information section, bold the statement "CREON® Capsules should always be taken with food," as this statement can be easily overlooked in all of the information presented.

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Acting Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
5/8/2007 05:10:37 PM



PDUFA GOAL DATE EXTENSION

NDA 20-725

Solvay Pharmaceuticals
Attention: Donald A. Ruggirello
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon[®] (pancrelipase) Delayed-Release Capsules 6, 12, and 24.

We also refer to your submission dated November 17, 2006, received on November 20, 2006, that included a complete response to our October 9, 2003, Not Approvable Letter.

On March 16, 2007, we received your March 15, 2007, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 17, 2007.

If you have questions, please call Maureen Dewey, Regulatory Project Manager at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, M.D, Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Harvey

4/24/2007 08:36:32 AM



NDA 20-725

INFORMATION REQUEST LETTER

Solvay Pharmaceuticals
Attention: Donald A. Ruggirello
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon[®] (pancrelipase) Delayed-Release Capsules 6, 12, and 24.

We also refer to your submission dated November 17, 2006 that included a complete response to our October 9, 2003 Not Approvable Letter.

We are reviewing the Microbiology and Regulatory section of your submission and have the following information requests:

Microbiology

Provide microbial limits sampling and testing protocols for the finished dosage form. The in-process testing in the sampling plan provided does not test the assembled dosage form. Refer to the *International Conference on Harmonisation (ICH); Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* as well as Decision Tree #8 for guidance on setting microbiological attributes for non-sterile dosage forms.

Regulatory

In accordance with 21 CFR 54.4, please include Financial Disclosure forms with authorized signatures for the following studies:

S245.2.003: "Cross-over pharmacology study to compare the duodenal lipase activity of two Creon[®] formulations in duodenal aspirates in subjects with pancreatic exocrine insufficiency due to chronic pancreatitis"

S248.3.003: "Open-label, Single-arm, Multicenter Study to Evaluate the Efficacy and Tolerability of Creon[®] for Children in Infants with Pancreatic Exocrine Insufficiency Caused by Cystic Fibrosis"

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff (CPMS)
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
4/9/2007 05:14:54 PM



NDA 20-725

INFORMATION REQUEST LETTER

Solvay Pharmaceuticals
Attention: Donald A. Ruggirello
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your November 17, 2006, new drug application (NDA) "Complete Response to Not Approvable Letter" submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon[®] (pancrelipase) Delayed-Release Capsules 6, 12, and 24.

We are reviewing the Clinical Pharmacology section of your submission and have the following information requests:

Clinical Pharmacology requests regarding study S245.2.003 titled, "Cross-over Pharmacology Study to Compare the Duodenal Lipase Activity of Two Creon[®] Formulations in Duodenal Aspirates in Subjects with Pancreatic Exocrine Insufficiency Due to Chronic Pancreatitis."

1. In your November 17, 2006 submission (Volume 15, p.5198, Section 9.1), you stated, "The lipase activity measured in this study (S245.2.003) was determined by an assay that used tributyrin (TC4) as substrate. Therefore, the absolute lipase activities in this study are not directly comparable to the lipase activities that would have been observed if the USP methodology was used. The USP methodology would have resulted in lower lipase activity compared to the TC4 methodology."

We noted in Study S245.2.003, the pancreatic lipase measured in the duodenum was more than 9,000 units for both formulations but the dose given was 6,000 units.

Please provide the conversion factor between your measured unit and the United States Pharmacopeia (USP) unit (i.e., one unit of pancreatic lipase (PL) activity determined by USP method is equivalent to how many units of PL activity determined by your assay). Please also include all supporting data.

2. Please explain the difference in PL activity between overall PEG-corrected (mean: (b) (4) for the To-be-Marketed Product (TbMP); Table 12) and total PEG-corrected (mean (b) (4) for TbMP; Table 13) and the difference between those for the Currently Marketed Product (CMP). Please refer to the data reported in Table 12 (Vol.15, p.5183) and Table 13 (Vol. 15, p.5184).

3. In Volume 15, p. 5183, you stated, "As indicated in the study protocol, this parameter showed a high variability between subjects. Within subjects, the variability was less pronounced. The summary by treatment sequence and period shows no major change in time (see Table 41, p. 168). However, mean values were more than twice as high for subjects randomized to the treatment sequence TbMP/CMP than for subjects randomized to CMP/TbMP."

Please explain the difference in the PL activities, which were approximately three fold higher (not just two fold) for the TbMP/CMP sequence than those for the CMP/TbMP sequence. (Volume 15, pp. 5461-5456, Table 59).

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, please call Maureen Dewey, Regulatory Health Project Manager at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff (CPMS)
Safety Regulatory Project Manager (SRPM)
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
4/3/2007 12:29:50 PM



NDA 20-725

INFORMATION REQUEST LETTER

Solvay Pharmaceuticals
Attention: Donald A. Ruggirello
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your November 17, 2006, new drug application (NDA) "Complete Response to Not Approvable Letter" submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon[®] (pancrelipase) Delayed-Release Capsules 6, 12, and 24.

We are reviewing the Clinical Pharmacology and Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests:

Clinical Pharmacology

These requests are in regard to the capsules (Batch #69027 and #69028) used in the intubation study titled "Cross-over pharmacology study to compare the duodenal lipase activity of two Creon formulations in duodenal aspirates in subjects with pancreatic exocrine insufficiency due to chronic pancreatitis" (Study S245.2.003).

1. Please clarify if lot 69027 and lot 69028 in Study 245.2.003 are filled at overage or 100% label-claim, and explain the discrepancy of the activity of lot 69027. (Submission dated November 17, 2006, Volume 4, pages 1108 and 1132).
2. Please indicate the assay results for these two batches at the time of product release and/or immediately before the conduct of Study S245.2.003.

Chemistry, Manufacturing and Controls

1. Please provide summary data from your drug substance and drug product process validations studies (including process characterization studies) that support your risk assessment approach to process validation. Supporting data should be included to establish all process controls, performance and operating parameters.
2. Explain the difference of drug substance batches grouped by "N" and "S" made by Solvay, and batches 85 and 115 made by Scientific Protein Labs (SPL).

3. Provide the drug substance lots used in manufacturing, the drug product validation lots and lots used to support the proposed expiration dating period.
4. Please provide standard procedures and investigation results on all manufacturing failures and rejected lots.
5. Provide current stability data on drug substance and product lots made in 2006, and the trend of all stability data to give the 95% confidence interval about the trending line.
6. Please provide stability data of drug product filled at 100% of the label claim of lipase activity.
7. Please explain the difference in (b) (4) activity in the drug substance comparison study titled "Cross-over pharmacology study to compare the duodenal lipase activity of two Creon formulations in duodenal aspirates in subjects with pancreatic exocrine insufficiency due to chronic pancreatitis" (Study S245.2.003) between SPL and Solvay, and the impact of (b) (4) activity on the safety and efficacy of final drug product. (Submission dated November 17, 2006, Volume 2, page 349).
8. Provide HPLC chromatograms and SDS-PAGE results of drug substance lots 0376, 0367, and 0115, and representative drug product lots of different strengths (6000, 12000, and 24000 USP units of lipase activity).

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, please call Maureen Dewey, Regulatory Health Project Manager at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff (CPMS)
Safety Regulatory Project Manager (SRPM)
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
3/30/2007 09:35:52 AM
Signing for Julie DuBeau.



NDA 20-725

INFORMATION REQUEST LETTER

Solvay Pharmaceuticals
Attention: Donald A. Ruggirello
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your November 17, 2006, new drug application (NDA) "Complete Response to Not Approvable Letter" submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon[®] (pancrelipase) Delayed-Release Capsules 6, 12, and 24.

We are reviewing the Microbiology, Statistical, Chemistry, Manufacturing and Controls, Clinical Pharmacology, and Labeling sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Microbiology

1. Identify the sampling process and method used to test the Creon[®] capsules for microbial limits [REDACTED] (b) (4)
2. Provide a data summary of studies that verify the suitability of the microbial limits methods for testing the Creon[®] capsules.

Statistics

3. For your study entitled, "A Double-blind, Multi-center, Randomized, Parallel Group Comparative Study to Prove Superior Efficacy of SA-001 versus Placebo in Patients with Pancreatic Exocrine Insufficiency Caused by Chronic Pancreatitis or Pancreatectomy" (study number S245.3.115), submit the following:
 - a) Your amended protocol submitted August 6, 2002.
 - b) A list of the 41 subjects assessed as evaluable and used to determine that the study was underpowered with the originally specified sample size of 15 subjects per group. Also provide the condition of the patient (e.g., patient had chronic pancreatitis or patient had a pancreatectomy.)

Chemistry, Manufacturing and Controls

4. Provide characterization information for the olive oil used in your lipase activity assay. Provide information on the routine qualification of the lots of olive oil to ensure the consistency of the assay results.
5. Tighten the acceptance criteria used in the specifications and consider implementing adequate controls to improve the manufacturing process. The very wide ranges of acceptance criteria for the enzymatic activities assays used in drug substance release and stability testing are not appropriate for approved therapeutic enzymes. Drug substance lots used in manufacturing of drug product need to be consistent to ensure safety and efficacy.
6. Demonstrate that other components in drug substance and product, including impurities and excipients, do not interfere with your enzymatic assay method. Relatively pure lipase or USP standard should be spiked into your drug substance and product. The increased activity should be proportional to the amount of enzyme activity added and measured independently.
7. A ^{(b) (4)} overage to compensate for drug product shelf life is not acceptable. Drug product stability acceptance criteria must be the same as the release acceptance criteria. Please propose an expiry dating period that satisfies this requirement.
8. Please set a specification for porcine parvovirus (PPV) which has been detected in drug substance.

Clinical Pharmacology

9. Please provide 90% confidence intervals (CI) for your study entitled, "Cross-over Pharmacology Study to Compare the Duodenal Lipase Activity of Two Creon[®] Formulations in Duodenal Aspirates in Subjects with Pancreatic Exocrine Insufficiency Due to Chronic Pancreatitis" (study number S245.2.003) in addition to the 95% confidence intervals you provided previously.

Labeling

10. The following issues/deficiencies have been identified in your proposed labeling.

Highlights Section:

- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
- Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an

established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

- Remove the period after the required statement “**See 17 for PATIENT COUNSELING INFORMATION**”. [21 CFR 201.57(a)(14)]
- A revision date must appear at the end of the highlights. However, for a new NDA, the revision date should be left blank at the time of submission and will be edited to the month/year of application approval. Please delete “Revised: 10/2006”. [21 CFR 201.57(a)(3)]
- A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].

Full Prescribing Information (FPI):

- Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous as the title for a subsection heading.
- The preferred format for presenting the titles of tables is without all capital letters.
- Do not refer to adverse reactions as “adverse events.” [see Section 6.6] Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
- The manufacturer information should be located after Patient Counseling Information section, at the end of labeling. [21 CFR 201.1]
- Please delete the company website (www.solvaypharmaceuticals-us.com) under the [Marketed By] section.
- Please change the subheading to title case **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**, not **13.1 Carcinogenesis, Mutagenesis, Impairment Of Fertility**. [See 21 CFR 201.57(c)(14)]

- Avoid using promotional terms [REDACTED] ^{(b) (4)} under section **[14 CLINICAL STUDIES]**.
- Patient Counseling Information must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)] Please use command language and provide subheadings and numbering for each item in this section. **[See 17 for PATIENT COUNSELING INFORMATION]**.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager
(301) 796-0845.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff (CPMS)
Safety Regulatory Project Manager (SRPM)
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
3/5/2007 04:27:11 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-725

Solvay Pharmaceuticals, Inc.
Attention: Donald A. Ruggirello
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

We acknowledge receipt on November 20, 2006 of your November 17, 2006 resubmission to your new drug application for Creon[®] (Pancrelipase Delayed-Release Capsules) 6, 12, and 24.

We consider this a complete, class 2 response to our October 9, 2003, action letter. Therefore, the user fee goal date is May 18, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any question, please call me at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Maureen Dewey
12/4/2006 01:56:18 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-725

Solvay Pharmaceuticals, Inc.
Attention: Karen Quinn, Ph.D.
Manager, CMC Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Dr. Quinn:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon[®] (Pancrelipase Delayed-Release) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on November 22, 2004 to discuss your intended responses to the deficiencies identified in your NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-9333.

Sincerely,

{See appended electronic signature page}

Monika Houstoun, Pharm.D.
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING

MEETING DATE: November 22, 2004
TIME: 11:00 AM - 12:30 PM
LOCATION: Conference Room B (Parklawn)
APPLICATION: NDA 20-725: Creon[®] (pancrelipase Delayed-Release Capsules, USP)
TYPE OF MEETING: Chemistry Advice (Type C)
MEETING CHAIR: Dr. Ruyi He
MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGICDP; HFD-180)

Kathy Robie-Suh, M.D., Ph.D., Hematology Team Leader
Ruyi He, M.D., Gastrointestinal Medical Team Leader
Hugo Gallo-Torres, M.D., Ph.D., Gastrointestinal Medical Team Leader
Fathia Gibril, M.D., Medical Officer
Diane Moore, Regulatory Health Project Manager
Jasti Choudary, B.V.Sc., Ph.D. – Supervisory, Pharmacologist

Division of New Drug Chemistry II (DNDC II)

Eric Duffy, Ph.D., Director
Blair Fraser, Ph.D., Deputy Director
Liang Zhou, Ph.D., Chemistry Team Leader
Ramesh Raghavachari, Ph.D., Chemist
Maria Ysern, M.S., Chemist
Martin Haber, Ph.D., Chemist

Office of Clinical Pharmacology and Biopharmaceutics (OCPB; HFD-870)

Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Solvay Pharmaceuticals Inc.

Karen Quinn, Ph.D., Manager, U.S. Regulatory Affairs

Steven Caras, M.D. Ph.D., Director of Clinical Development Gastroenterology, US

Solvay Pharmaceuticals GmbH, Germany

Hans Koch, Ph.D. Project Management, Marketed Product Support Enzymes
Guido Ruesing, Ph.D., Manager, Production Quality Services
Siegfried Schaefer, Ph.D., Senior Vice-President, Marketed Product Support
Guenter Krause, M. D., Head Clinical Development Gastroenterology, Europe
George Shlieout, Ph.D., Head of Dosage Form Development - Enzymes
Andreas Koerner, Ph.D., Head of Pharmaceutical Support
Andreas Potthoff, Ph. D., Manager, Enzyme Analytics, Marketed Product Support

BACKGROUND:

On July 31, 1997, (received August 1, 1997) Solvay Pharmaceuticals submitted NDA 20-725 for Creon. 5, 10 and 20 Minimicrospheres® (pancrealipase delayed-release capsules, USP) for treatment of adult and pediatric patients with exocrine pancreatic insufficiency. This condition is often associated with, but not limited to, cystic fibrosis, chronic pancreatitis, postpancreatectomy, post-gastrointestinal by-pass surgery or ductal obstruction of the pancreas or common bile duct. The application was filed September 30, 1997.

The sponsor was placed under the Application Integrity Policy (AIP) on September 24, 1997, and review of the Creon NDA was suspended. The Agency revoked the AIP status for Solvay on April 9, 2003.

On June 6, 2003, DGCDP sent Solvay Pharmaceuticals Inc. (Solvay) an information request letter requesting clinical and chemistry and manufacturing information. On July 9, 2003, Solvay submitted a very preliminary outline in response to the chemistry information requests in the Agency's June 6, 2003, letter.

On August 20, 2003, DGCDP sent Solvay a chemistry discipline review letter delineating 20 additional deficiencies in the NDA. A separate letter was sent to the DMF holder on August 14, 2003.

On August 22, 2003, Solvay requested a teleconference with the Agency to clarify some of the items in the August 20, 2003, agency letter. On August 25, 2003, representatives from Solvay and DGICDP held a teleconference to discuss the CMC issues listed in the August 20, 2003, Agency letter.

On October 9, 2003, DGCDP sent Solvay a not approvable letter for NDA 20-725. On October 30, 2003, representatives from Solvay and DGCDP held a teleconference to discuss the characterization of the drug substance reference standards and enzyme assays preliminary specification setting.

On November 20, 2003, representatives from Solvay and DGICDP held a teleconference to discuss the CMC issues concerning the proposed specifications for the drug substance and the drug product.

On September 7, 2004, Solvay submitted a meeting request to discuss Solvay's intended responses to the deficiencies identified for NDA 20-725. A background package was submitted on September 21, 2004.

Responses to the questions posed by the sponsor were faxed to the sponsor on November 18, 2004.

MEETING OBJECTIVE:

To update the Agency concerning the progress of the work by Solvay to address the deficiencies previously identified by the Agency for NDA20-725 and to obtain feedback from the agency concerning Solvay's proposals and plans for addressing these deficiencies.

DISCUSSION POINTS:

Drug Substance:

1. Solvay requests feedback from the Agency on whether the proposed drug substance specifications are acceptable and address all the appropriate deficiencies identified in the NDA.

FDA Response:

Specifications cannot be fully evaluated until characterization studies are concluded. Based on consideration of the data provided, we have the following comments:

(b) (4)



- **Regarding potency assays, upper and lower limits are needed.**

(b) (4)



- **Further discussion of characterization studies may be appropriate. A request for a CMC meeting should be made.**

Pancrelipase Sources and Comparability Protocols:

2. Solvay requests feedback from the Agency concerning the acceptability of our proposed comparability protocol for the characterization of the two sources of drug substance.

Solvay intends to submit documentation to the NDA for an alternate source of drug substance (European sourced pancrelipase referred to as Solvay Pancrelipase). If this alternate source is found acceptable to the Agency can approval of the drug product in our NDA be provided for each drug substance source independently?

FDA Response:

The comparability protocol cannot be fully evaluated until characterization studies are concluded.

Drug Product:

Linkage of Proposed Marketed Formulation to CMC Changes:

3. Before the start of the comparability study, Solvay seeks feedback from the Agency on both the method selection and the preliminary acceptance limits for this linking protocol, and on the acceptability of this approach to show the link from the drug product used in the clinical studies to the to-be-marketed product.

FDA Response:

[Redacted] (b) (4)

You need to do a bridging study in patients with exocrine pancreatic insufficiency to compare the products. Please submit your proposed protocol to the IND for comments.

An essentially completely new product (involving [Redacted] (b) (4) reformulation, aluminum packaging, new labeling and using a new drug substance) is proposed. The chemical comparison follows previous recommendations from the FDA but it cannot be fully evaluated until characterization studies are concluded.

Specifications:

4. Solvay requests feedback from the Agency on whether the proposed drug product specifications are acceptable and address all the appropriate deficiencies identified in the NDA.

FDA Response:

The revised drug product specifications follow previous recommendations from the Agency. The revised formulation attempts to duplicate the activities present in the capsules used for clinical trials as closely as possible. Specifications cannot be fully evaluated until characterization studies are concluded.

The dissolution method should include a test of the enteric coating (i.e., two stage dissolution test).

Data to Support Use of CREON in Children under Age of Seven:

5. Solvay requests from the Agency feedback concerning the acceptability of this data to support this use.

FDA Response:

The acceptability of the data to support the use in pediatric patients is a review issue. However, from the summary you have provided it appears that data for age < 3 years old are not included.

Due to our concerns regarding product degradation, additional clinical information is needed. For each patient, provide the date of enrollment, the duration of treatment, and the dose administered per day per protocol for all clinical trials. Based upon stability data, provide an estimate of actual enzyme administered (lipase, protease, amylase) to each patient in the clinical trials. These data will provide the corrected dose due to batch degradation at the time of treatment. In addition, you should provide complete formulation information for the drugs used in the pediatric study.

Sprinkling:

6. Solvay requests from the Agency feedback concerning the acceptability of this data to support this use.

FDA Response:

You need to submit *in vitro* stability data in support of the use of sprinkled Creon pellets on specific foods (e.g., applesauce, apple juice). If the in-vitro study does not

demonstrate identical stability to that of the intact capsules, you may need to demonstrate *in vivo* comparability of Creon Capsules when administered as sprinkled pellets and intact Capsules using duodenal aspiration data. Provide rationale for the selected approach.

General Discussion:

7. Submission Timelines and Stability Data Considerations: Solvay would like to discuss our timelines concerning the submission of our complete response. Additionally we would like to discuss the required stability data of the “to-be-marketed” drug product to be included in the response.

Will Solvay's response to the action letter of 9 October 2003 be considered a Class II resubmission with a 6 month target review time? If so can Solvay provide nine months of the "to be marketed" drug product stability at time of submission, then update the submission with the 12 month stability data during the review time? We would agree to provide the 12 month data at least three months before the review target date. Would this be acceptable? Additionally Solvay would like to know if it would be possible to submit some of the CMC responses of final information before the final response (rolling CMC submissions)?

FDA Response:

We would consider a complete response to the action letter as a Class II resubmission. However, with regard to stability data, you should submit all stability data available at the time of submission of the amendment and provide additional data as it becomes available.

We recommend you submit an amendment identifying the proposed new Solvay source of the API and associated testing facilities and responsibilities. CFN numbers should be provided, if available.

ACTION ITEMS:

- Solvay will establish a two-sided limit for potency assays for the drug substance.
- Solvay will be ready for inspection of the alternate facility for preparing raw substances.
- Solvay will submit the following:
 - Complete characterization of the Drug Substance.
 -  (b) (4)
- An amendment to add the Solvay alternate facility for Drug Substance to initiate a facility inspection.

- A draft proposal for a bridging study between the old and new formulations with two animal species and a human study or a proposal for a different *in- vivo* study.
- Available data on pediatric patients.
- *In-vitro* stability data in support of the use of sprinkled Creon pellets on specific foods
- Meeting requests for further discussion of characterization studies.

Minutes Preparer: _____
Monika Houstoun, Pharm.D.
Regulatory Project Manager

Chair Concurrence: _____
Ruyi He, M.D.
Medical Team Leader

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

/s/

Monika Houstoun
12/16/04 05:57:33 PM

Ruyi He
12/16/04 06:10:54 PM



NDA 20-725

Solvay Pharmaceuticals, Inc.
Attention: Karen Quinn, Ph.D.
Manager, CMC Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Dr. Quinn:

Please refer to the meeting between representatives of your firm and FDA on November 11, 2003. The purpose of the meeting was to discuss the proposed drug substance and drug product specifications for Creon.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Diane Moore
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE

MEETING DATE: November 20, 2003

TIME: 11:00 AM - 12:00 PM

LOCATION: Room 6B-45 (Parklawn)

APPLICATION: NDA 20-725; Creon (pancrelipase) Capsules

TYPE OF MEETING: Guidance; Chemistry, Manufacturing, Quality Control (CMC)

MEETING CHAIR: Dr. Martin Haber

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGCIDP; HFD-180)

Diane Moore, Regulatory Health Project Manager
Alice Kacuba, R.N., RAC, Regulatory Health Project Manager
Monika Houstoun, Pharm. D., Consumer Safety Officer

Division of New Drug Chemistry II (DNDC II)

Liang Zhou, Ph.D., Chemistry Team Leader
Martin Haber, Ph.D., Chemist

EXTERNAL CONSTITUENT ATTENDEES AND TITLE:

Solvay Pharmaceuticals, Inc. Baudette, MN

Karen D. Quinn, Ph.D., Manager, U.S. Regulatory Affairs, CMC

Solvay Pharmaceuticals GmbH, Germany

Hans Koch, Ph.D. Project Management, Marketed Product Support Enzymes
Dieter Franke, Ph.D., Head, QA/QC, Neustadt Manufacturing
Claus-Juergen Koelin, Ph.D., Head, Manufacturing Bulk Material & API
Kathrin Rother, MsC, Manager, Europe Regulatory Affairs-CMC Compliance
Guido Ruesing, Ph.D., Manager, Production Quality Services

BACKGROUND:

On July 31, 1997, (received August 1, 1997) Solvay Pharmaceuticals submitted NDA 20-725 for Creon[®] 5, 10 and 20 Minimicrospheres[®] (pancrealipase delayed-release capsules, USP) for treatment of adult and pediatric patients with exocrine pancreatic insufficiency. This condition is often associated with, but not limited to, cystic fibrosis, chronic pancreatitis, post-pancreatectomy, post-gastrointestinal by-pass surgery or ductal obstruction of the pancreas or common bile duct. The application was filed September 30, 1997. The sponsor was placed under the Application Integrity Policy (AIP) on September 24, 1997, and review of the Creon NDA was suspended. The Agency revoked the AIP status for Solvay on April 9, 2003.

On June 6, 2003, DGCDP sent Solvay Pharmaceuticals Inc. (Solvay) an information request letter requesting clinical and chemistry and manufacturing information. On July 9, 2003, Solvay submitted a very preliminary outline in response to the chemistry information requests in the Agency's June 6, 2003, letter. On August 20, 2003, DGCDP sent Solvay a chemistry discipline review letter delineating 20 additional deficiencies in the NDA. A separate letter was sent to the DMF holder on August 14, 2003. On August 22, 2003, Solvay requested a teleconference with the Agency to clarify some of the items in the August 20, 2003, agency letter. On August 25, 2003, representatives from Solvay and DGICDP held a teleconference to discuss the CMC issues listed in the August 20, 2003, Agency letter. On October 9, 2003, DGCDP sent Solvay a not approvable letter for NDA 20-725. On October 30, 2003, representatives from Solvay and DGCDP held a teleconference to discuss the characterization of the drug substance reference standards and enzyme assays preliminary specification setting.

On November 5, 2003, Solvay requested a CMC teleconference to discuss specific questions concerning the proposed specifications for the drug substance and the drug product. The background information was included in the meeting request.

MEETING OBJECTIVE:

To discuss the proposed drug substance and drug product specifications for Creon.

DISCUSSION POINTS:

In response to the questions in the November 5, 2003, list of questions, the following discussion ensued. The format provides the firm's questions in italics, followed by DGCDP's responses in bolded lettering, followed by further comments.

Question 1:

Summary by Solvay of the report "Options for Blending Pancreatin and Specification Setting of CREON[®] capsules for the US." This report had been previously provided in Solvay's submission of 16 July 2003. The report has been updated and is provided in Attachment 1. The update corrected the upper range for recovery of Free Protease in the table on page 7. Additionally a

table was added to page 7 to provide more clarification on how the data were derived. The final data, proposed specification ranges and percent usage, remain the same.

FDA Response:

We acknowledge the information.

Question 2:

Solvay requests guidance on the Agency's preference for the proposed options for setting specifications for enzyme levels. Based on the limitations discussed in the above report, would the Agency prefer that Solvay focus on a tighter range of specification for Lipase (b) (4) with consequently a larger range for Amylase and Protease (b) (4) or would the Agency prefer that all of the enzyme's specification ranges be equally tightened (b) (4)?

FDA Response:

Regarding specifications for enzyme levels in the drug product, final recommendations will depend on setting good drug substance specifications. When the drug substance specifications have been revised, then the drug substance limits can be discussed further. In general, the lipase may be the most important to control but we will need clinical team input regarding acceptable limits for amylase and protease. Regarding the formulation, the upper limit of (b) (4) for lipase activity is not intended to encourage a stability overage.

Comments:

- Solvay asked if the Drug Substance specifications for the enzyme levels might be revised.
- The Division notes that Solvay should refer to the specific questions regarding revisions to enzyme levels in the June 6 and August 20, 2003, Agency letters. In general, we request updated specifications for the Drug Substance enzyme levels. Additions to the specifications may be needed. We prefer to limit the range for lipase rather than adopt broad levels for all enzymes. Because data from the manufacturing process used by the DMF holder for the drug substance is needed to determine enzyme specifications for the drug product, it is premature to discuss details regarding drug product specifications or blending ranges for specific batches. You need to work with the DMF holder and drug substance supplier so that the issues regarding the drug substance are addressed. This also applies to the characterization issue. The (b) (4) upper limit is not intended to allow for losses during stability.
- The sponsor clarifies that they do not mean to intend a (b) (4) overage. Refer to option 1 in the report included in the background package where overage is (b) (4) for analytical and fill-weight variability. Actual production losses are unknown.

- The Agency notes that production losses were not included in the background package. You should keep a running average of a target enzyme and calculate the enzyme losses. You should remove the reference to stability overage and indicate the variability in (b) (4); allowed to (b) (4). You also need to tighten ranges on enzymes, focusing on the lipase levels first.

Question 3.

Solvay would like to propose a specification for Total Proteases instead of for Free Proteases. Is this acceptable to the Agency? Reference is made to Solvay's response of 21 October 2003 (Attachment 4) to the Agency's request (correspondence of 20 August 2003, item 3).

FDA Response:

Regarding replacing the Free Proteases specification with one for Total Proteases, we would prefer determination of both free and total. Regarding the 10/21/03 amendment, there is a typographical error on p. 16; is it correct that free proteases are (b) (4) of the total?

Comments:

- Solvay confirms that free proteases are (b) (4) of the total proteases. Solvay notes that there is not a constant ratio between the free and total proteases.
- The Agency recommends that Solvay set separate limits for both free and total proteases based upon the worst case scenario on both ends. Solvay should test both total and free proteases and, if necessary, set a specification for either total or free protease and monitor that specification. This approach should be adequate initially, but will be reviewed for adequacy upon submission. Solvay should collect the data and make their argument on the proposal that gives the most information.
- Solvay needs to work with the DMF holder to calculate a compensation for loss, revise the broad specification for drug substance, set up tests for free and total proteases, and plan responses to all drug substance deficiencies.

Question 4:

Are the proposed specifications for the residual solvents- (b) (4) acceptable? Reference is made to Solvay's response of 21 October 2003 (Attachment 11) to the Agency's request (correspondence of 20 August 2003, item 10).

FDA Response:

Regarding residual solvents, based on the batch data submitted, it should be possible to tighten the acceptance limits for (b) (4) from those proposed. Only one lot in each case was at the level proposed. We will need to consult with the FDA Pharmacologist/Toxicologist regarding safe levels.

Comment:

The Q3C Guidance for Industry entitled "Impurities: Residual Solvents" dated December 1997, recommends less than 50 mg per day for these types of total residual solvents. Based on batch data submitted, the mean limit for (b) (4) is (b) (4) mg and the mean limit for (b) (4) is (b) (4) mg. Tighten your specifications for (b) (4) and (b) (4). Show no impact on enzyme action based on batch data. The final limits are review issues.

Question 5:

Are the proposed specifications for microbial limits acceptable? Reference is made to Solvay's response of 21 October 2003 (Attachment 16) to the Agency's request (correspondence of 20 August 2003, item 15).

FDA Response:

Regarding microbial limits, the mean total aerobic count from several batches was (b) (4). What is the standard deviation? The proposed limit of (b) (4) appears to be too high.

Comment:

In Attachment 16 of the background package, the mean total aerobic count is (b) (4) mean value per gram. The sponsor calculates the standard deviation as (b) (4) colony units (cfu)/gm. The sponsor's revised proposed limit of (b) (4) for the total aerobic count is a review issue.

Question 6:

Are the proposed particle size specifications for the minimicrospheres acceptable? Reference is made to Solvay's response of 21 October 2003 (Attachment 12) to the Agency's request (correspondence of 20 August 2003, item 11).

FDA Response:

Regarding particle size specifications for minimicrospheres, what is the mean particle size? Is it possible to tighten the limits to NMT (b) (4) above and below the indicated sizes? How were the screen sizes chosen for testing?

Comment:

- The sponsor has no data on the mean particle size for the mini-microspheres. The sponsor proposes to change (b) (4)

- Submit more data on the particle size. Check the Guidance for Industry entitled "SUPAC-MR: Modified Release Solid oral Dosage forms Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls; *In Vitro* Dissolution Testing and *In Vivo* Bioequivalence Documentation" for changes in particle size. Assess previous manufacturer batches used in the clinical study and future to-be-marketed batches. The changes must be consistent with historical batches and clinical trial batches. The final specifications will be a review issue.

Additional Comment:

Solvay requests a future teleconference to discuss additional items from the Oct 9, 2003, letter. The Agency reminds Solvay, in the future, when requesting a meeting or teleconference with the Division on this NDA, you need to submit a more comprehensive background package. A piece-meal approach to the questions makes it difficult to review the submitted information. Consider consolidating future submissions so that more than a few questions can be settled at one meeting.

CONCLUSIONS:

- Solvay should do the following:
 - Remove the reference to stability overage and indicate the variability in blending allowed to (b) (4).
 - Tighten ranges on enzymes, focusing on the lipase levels first.
 - Set separate limits for both free and total proteases based upon the worst case scenario on both ends. Alternatively, test both total and free proteases and set a specification for either total or free protease and monitor that specification, with justification.
 - Collect the data and make their argument on the proposal that gives the most information.
 - Work with the DMF holder to calculate a compensation for loss; revise the broad specifications for the drug substance, set up tests for free and total proteases, and plan responses to all drug substance deficiencies.
 - Tighten the specifications for residual (b) (4) and show no impact on enzyme activity based on batch to batch data.
 - Limit total aerobic count to (b) (4) units/gm.
 - Submit data on particle size for minimicrospheres.
 - For additional questions regarding the drug substance or drug product, submit a comprehensive background package covering the entire plan you propose to implement to address the issues from the October 9, 2003, action letter.

ACTION ITEMS: none.

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

/s/

Diane V. Moore
12/2/03 06:29:28 PM

Martin Haber
12/3/03 10:00:42 AM



NDA 20-725

Solvay Pharmaceuticals, Inc.
Attention: Karen Quinn, Ph.D.
Manager, Regulatory Affairs, CMC
901 Sawyer Road
Marietta, GA 30062

Dear Dr. Quinn:

Please refer to the meeting between representatives of your firm and FDA on October 30, 2003. The purpose of the meeting was to discuss the status of characterization studies and other CMC issues pertaining to Creon[®] Minimicrospheres[®] (pancrealipase delayed-release capsules, USP).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Diane Moore, B.S.
Regulatory Project Manager
Division of Gastrointestinal & Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 30, 2003

TIME: 10:00 AM – 11:00 AM

LOCATION: Parklawn Building, (Dr. Haber's office, Room 14B-45)

APPLICATION: NDA 20-725
Creon® Minimicrospheres® (pancrealipase delayed-release capsules, USP)

TYPE OF MEETING: Type A: CMC advice

MEETING CHAIR: Dr. Martin Haber

MEETING RECORDER: Mr. Ryan Barraco for Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Martin Haber, Ph.D.	Chemist	Division of New Drug Chemistry (DNDC II) co-located with the Division of Metabolic and Endocrine Products (DMEDP) (HFD-510)
2. Ryan Barraco, B.A., B.S.	Consumer Safety Officer	Division of Gastrointestinal and Coagulation Drug Products (DGCDDP) (HFD-180)

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Solvay Pharmaceuticals, Inc. Baudette, MN

<u>External Attendee</u>	<u>Title</u>
1. Karen D. Quinn, Ph.D.	Manager, Regulatory Affairs, CMC

Solvay Pharmaceuticals GmbH, Germany

<u>External Attendee</u>	<u>Title</u>
1. Hans Koch, Ph.D.	Project Management, Marketed Product Support Enzymes
2. Andreas Potthof, Ph.D.	Manager, Enzyme Analytics
3. Bernd Thumbek, Ph.D.	Pharmaceutical Analysis, Marketed Products
4. Andreas Koerner, Ph.D.	Head Pharmaceutical Support, Marketed Products
5. Guido Ruesing, Ph.D.	Manager, Production Quality Services

BACKGROUND:

On July 31, 1997, (received August 1, 1997) Solvay Pharmaceuticals submitted NDA 20-725 for Creon[®] 5, 10 and 20 Minimicrospheres[®] (pancrealipase delayed-release capsules, USP) for treatment of adult and pediatric patients with exocrine pancreatic insufficiency. This condition is often associated with, but not limited to, cystic fibrosis, chronic pancreatitis, post-pancreatectomy, post-gastrointestinal by-pass surgery or ductal obstruction of the pancreas or common bile duct. The application was filed September 30, 1997. The sponsor was placed under the Application Integrity Policy (AIP) on September 24, 1997, and review of the Creon NDA was suspended. The Agency revoked the AIP status for Solvay on April 9, 2003.

On June 6, 2003, DGCDP sent Solvay Pharmaceuticals Inc. (Solvay) an information request letter requesting clinical and chemistry and manufacturing information. On July 9, 2003, Solvay submitted a very preliminary outline in response to the chemistry information requests in the Agency's June 6, 2003, letter. On August 20, 2003, DGCDP sent Solvay a chemistry discipline review letter delineating 20 additional deficiencies in the NDA. A separate letter was sent to the DMF holder on August 14, 2003. On August 22, 2003, Solvay requested a teleconference with the Agency to clarify some of the items in the August 20, 2003, agency letter. On August 25, 2003, representatives from Solvay and DGICDP held a teleconference to discuss the CMC issues listed in the August 20, 2003, Agency letter. On October 9, 2003, DGCDP sent Solvay a not approvable letter for NDA 20-725. On October 21, 2003, Solvay requested a teleconference with DGCDP to discuss the CMC items listed in the October 9, 2003, not approvable letter.

MEETING OBJECTIVES:

To discuss items listed in the October 9, 2003, Agency not approvable letter to NDA 20-725.

DISCUSSION POINTS:

- Brief Summary from Solvay concerning status of characterization studies (refer to report D0004911 in Attachment 22 of October 21, 2003 background package) including Solvay's proposed plan for characterization and specification setting and their most recent results.

DECISIONS:

In response to the questions in the October 21, 2003, background package, the following agreements were reached after discussion. The format provides the firm's questions followed by DGCDP's responses in bold lettering.

- Questions Concerning Characterization Studies: Is the set of analytical methods as described in D0004911 acceptable for the agency for the purposes of characterization and comparability testing of the API as well as the drug product? For specification setting, we intend to use one of these methods, e.g. SDS-PAGE or HPLC, as an additional release testing item for unambiguous identification and testing compliance of enzyme pattern to the specification. Would this approach be acceptable to the Agency?

Agency Response and Discussion with Solvay:

- **Regarding the set of analytical methods used for drug substance characterization,** (b) (4)

[Redacted]

(Faxed to the firm October 29, 2003)

- **Dr. Haber also asked about the quantities of each enzyme and Solvay stated they had not addressed that issue. Dr. Haber responded by stating that it is important to know what enzymes are in the drug substance and their activities. Through more discussion it was clarified that Dr. Haber wanted the best estimate of the** (b) (4)

[Redacted]

- [Redacted] (b) (4)
- [Redacted]
- [Redacted]

(b) (4)

Agency Response and Discussion with Solvay:

- **Regarding reference standards, the plan for the primary reference standard using (b) (4) enzymes sounds good. We can discuss the plan for secondary standards further as the description in the question is unclear to me. Probably some arrangement for internal/working standards will need to be arranged since commercial standards may not always be available. (Faxed to the firm October 29, 2003)**

- **Dr. Haber asked for clarification on the plan for the secondary standards. Solvay explained that they plan (b) (4)**

Karen Quinn clarified by stating that (b) (4) they are looking at. Dr. Haber stated that the secondary reference standard must be well characterized, and that the plan sounds reasonable. Karen Quinn clarified that in Dr. Haber's opinion, the (b) (4), (b) (4)) was not an ideal primary reference standard and that it would have to be well characterized. Solvay stated that their (b) (4) Dr. Haber clarified by stating that Solvay may have to investigate alternative primary standards from multiple sources. Solvay asked if multiple sources meant different suppliers and Dr. Haber confirmed.

- **Question Concerning Protease Assay: It was requested to establish specific assays for e. (b) (4) and Solvay is intending to establish such kind of enzymatic assays to the extent possible. These methods will be used for (b) (4)**

(b) (4)

Agency Response and Discussion with Solvay:

- **Regarding the protease assay, the less specific (b) (4) protease assay might be feasible for release if it can be shown to accurately represent some or most of the enzyme activity present. Additional tests may be required. In general, there are (b) (4)**

(Faxed to the firm October 29, 2003)

- **Dr. Haber, after outlining the above response,** [REDACTED] (b) (4)
[REDACTED] **and may not be possible, but that Solvay should try. Solvay stated that they would like to develop as specific assays as possible. Solvay stated that they did literature research for all substrates for all pancreatic proteases. Their intentions,** [REDACTED] (b) (4)
[REDACTED]

- **Solvay also asked if they could use enzyme from** [REDACTED] (b) (4)
[REDACTED]

- **Solvay then commented on the specification setting for** [REDACTED] (b) (4)
[REDACTED]

- **Dr. Haber then asked what the time frame would be before Solvay would respond. Karen Quinn stated that Solvay would like to have another teleconference for discussing specifications of the drug product and substance. Ryan Barraco stated that Solvay should send in a meeting request when they have prepared questions for the Agency. At this time, the teleconference was concluded.**

Minutes Preparer: _____
Ryan Barraco, B.A., B.S.
Consumer Safety Officer

Chair Concurrence: _____
Martin Haber, Ph.D.
Chemist

MEETING MINUTES

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

/s/

Ryan Barraco
11/6/03 12:10:22 PM
Signed for Ms. Diane Moore

Martin Haber
11/6/03 12:58:19 PM

14 pp withheld in full immed. after this page as (b)(4) CCI/TS.

MEMORANDUM OF TELECONFERENCE

MEETING DATE: August 25, 2003

TIME: 2:00 - 2:30 PM

LOCATION: Room 6B-45 (Parklawn)

APPLICATION: NDA 20-725; Creon[®] 5, 10, 20 Minimicrospheres (pancrelipase Delayed-Release Capsules, USP)

TYPE OF MEETING: Guidance; Chemistry, Manufacturing, Quality Control

MEETING CHAIR: Dr. Martin Haber

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGCIDP; HFD-180)

Diane Moore – Regulatory Health Project Manager

Division of New Drug Chemistry II (DNDC II)

Eric Duffy, Ph.D., Director
Liang Zhou, Ph.D., Chemistry Team Leader
Ali Al-Hakim, Ph.D., Chemist
Maria Ysem, M.S., Chemist
Martin Haber, Ph.D., Chemist

EXTERNAL CONSTITUENT ATTENDEE AND TITLE:

Solvay Pharmaceuticals Inc.

Karen Quinn, Ph.D., Manager, CMC Regulatory

BACKGROUND:

On July 31, 1997, (received August 1, 1997) Solvay Pharmaceuticals submitted NDA 20-725 for Creon[®] 5, 10 and 20 Minimicrospheres (pancrelipase delayed-release capsules, USP) for treatment of adult and pediatric patients with exocrine pancreatic insufficiency. This condition is often associated with, but not limited to, cystic fibrosis, chronic pancreatitis, post-pancreatectomy, post-gastrointestinal by-pass surgery or ductal obstruction of the pancreas or common bile duct. The application was filed September 30, 1997. The sponsor was placed

under the Application Integrity Policy (AIP) on September 24, 1997, and review of the Creon NDA was suspended.

On October 9, 1997, the Division sent the sponsor an information request letter. The sponsor submitted several amendments to the NDA between December 18, 1997 and December 16, 2002.

On March 22, 2002, the sponsor submitted a request that review of the NDA be resumed. In a letter dated November 21, 2002, the Division informed the sponsor that, after considering their request, the Division had concluded that an exception to the AIP was not warranted, and that review of the NDA would not resume until AIP status is revoked.

The Agency revoked the AIP status for Solvay on April 9, 2003.

On June 6, 2003, DGICDP sent Solvay Pharmaceuticals Inc. (Solvay) an information request letter requesting clinical and chemistry and manufacturing information. On July 9, 2003, Solvay submitted a very preliminary outline in response to the chemistry information requests in the Agency June 6, 2003, letter. On August 20, 2003, DGICDP sent Solvay a chemistry discipline review letter delineating 20 additional deficiencies in the NDA. A separate letter was sent to the DMF holder on August 14, 2003. On August 22, 2003, Solvay requested a teleconference with the Agency to clarify some of the items in the August 20, 2003, agency letter. Solvay sent the questions to DGICDP via telefacsimilie on August 25, 2003.

MEETING OBJECTIVE:

To clarify items listed in the August 20, 2003, agency letter to NDA 20-725.

DISCUSSION POINTS:

In response to the questions in the August 25, 2003, background package, the following discussion ensued. The format provides the FDA's comments from the August 20, 2003, letter, followed by the firm's questions in italics, followed by DGICDP's responses in bolded lettering.

- Question 1a: The Federation Internationale Pharmaceutique (FIP) reference standards for the drug substance are inadequate. *How are the FIP reference standards inadequate?*
 - **FDA Response:**
 - **The FIP reference standards need to be characterized for purity and identity.**
- Question 1b.: Develop appropriate well-characterized reference standards based on the results of identity and characterization studies of the drug substance. *Is the FDA requesting that we provide characterization data for the reference standard as we are planning for the drug substance? Would then the FIP standards be adequate?*

- **FDA Response:**
 - **You need to have separate, independent standards for each enzyme in the drug product.**

- Further Discussion:
 - The sponsor stated that separating the enzymes is very difficult and that the method takes a long time to develop.
 - The Agency reminds the sponsor that there have been literature references for separation methods for pancreatic enzymes since the 1960s. We request you research what has been attempted by your company and what is in the literature.
 - The sponsor agreed to discuss this aspect further with other areas of the company and determine what information is available on this topic. The sponsor may request further discussion at a later date.

- Question 2a: Regarding a protease assay, provide data demonstrating individual specificity for (b) (4). *Is the FDA asking us to determine if all of the four defined proteases work in the protease assay that was filed in the application?*

FDA Response:

- **You need a protease assay that is specific for each of the enzymes that are present in your drug substance, if possible for a mixture of enzymes. Tests to determine the identity, purity and quantity of each enzyme should be developed. Because the general assay filed in the NDA is not specific, you need other assays for the specific enzymes you have in the drug substance and product. You will need at least a fingerprint or defined profile of the enzyme composition of the drug substance. You must demonstrate what is present and that it is enzymatically active.**

- Question 2b.: We recommend the use of purified enzymes for reference. If specificity cannot be demonstrated, other assay methods may be required. The substrate should be well defined (source, sequence, mass, etc.). *Is this referring to the substrate in the current assay or to potential substrates used in other assay methods if required because specificity cannot be demonstrated?*

FDA Response:

- **The enzyme substrate is not well defined in the current assay submitted to the NDA. You need a well-defined substrate in any enzyme assay. The proteolytic specificity of the pancreatic proteases are known. With a substrate of known sequence, the predicted cleavage pattern should be confirmed, if possible in a mixture of enzymes.**

- **The sponsor claimed that purified enzymes that are commercially available are not very pure. However, the sponsor agreed to try to supply the requested information.**
- Question 2c.: In addition, define the product by a suitable method, i.e., HPLC. *What is meant by product here, are you referring to the substrate or the drug product?*

FDA Response:

- **We are referring to the product of the enzyme-catalyzed reaction. Both the substrate starting material and product should be chemically well defined.**
- Question 2d.: Provide method validation data. *Which method is being referred to here?*
 - **FDA Response:**
Refer to the API methods or drug substance methods that will be developed after characterization is complete.
 - **Sponsor Comment:**
 - **The sponsor proposes to perform drug product release testing and is seeking to cross-reference methods to the DMF.**
- Question 3a.: The substrate in the pancreatic lipase assay should be well characterized and well defined. Provide method validation data. *The method validation data for the lipase method is provided in the application, is this request referring to other method validation data?*
 - **FDA Response:**
 - **You should provide validation for the revised pancreatic lipase assay method that you will develop after characterization is complete.**
 - **The method validation for the lipase assay should demonstrate that the lipase assay appropriately analyzes a well-characterized and well-defined lipase enzyme in the drug substance and/or product.**
- Question 4.: Define the percentage of amylose in the substrate of your amylase assay. Provide a clear discussion of the basis for the assay, including stoichiometries for all reactions and a description of how the activity units are calculated. Provide method validation data. *The method validation data for the amylase method is provided in the application, is this request referring to other method validation data?*
 - **FDA Response:**
 - **You should provide validation for the revised amylase assay method that you will develop after characterization is complete.**

- **The method validation for the amylase lipase assay should demonstrate that the amylase assay appropriately analyzes a well-characterized and well-defined amylase enzyme in the drug substance and/or product.**

- Question 5: Provide full testing plan and complete stability protocol for the Creon Drug product. *This was provided in the current application, or is this referring to the new testing plan and stability protocol that will be submitted to support the new proposed DP specifications and new lots that have been requested to be put on stability?*
 - **FDA Response:**
Yes, provide the new testing plan.
 - **Because the Creon product is not well characterized, there is no established purity protocol on which to base adequate testing for impurities.**

- Question 6: Regarding the stability data for Creon capsules, provide graphical representations of the stability results for each enzyme activity as a function of storage time. Provide the slopes for linear fits to this data of all enzyme activities. *Are the graphical representations from the FDA program acceptable or would the FDA prefer better graphs?*
 - **FDA response:**
 - **You laid out testing and time points for Creon 5, Creon 10 and Creon 20 capsules in the NDA. Without validated tests, you cannot have a stability protocol using those tests. You should revise the stability protocol once the test methods are set. Revise the testing plan and stability protocol to demonstrate 100% of target parameters.**
 - **We prefer better graphs. You can modify the FDA program to produce better graphs. We prefer a clearer presentation from a chemical point of view rather than a statistical point of view.**

- Question 7: *Any feedback from the Agency concerning Solvay's responses of July 9, 2003 to CMC questions 1 and 2 for characterization proposed in the application for the drug substance and drug product?*
 - **FDA Response:**
There are a number of possible methods for characterizing the Drug Substance. You should discuss with the DMF holder what to do to address the deficiency. In general you are going in the right direction.

- Question 8: *Any feedback from the Agency concerning Solvay's responses of July 9, 2003 to CMC question 3 for the proposal concerning the label claim?*

- **FDA Response:**

You should reformulate to 100% of the label claim at the current level. (b) (4)

(b) (4) **We prefer the 100% label claim formulation where the physicians are familiar with the product at the doses they generally use. If we change the dosage, it will cause confusion in the marketplace. We conclude that it is best to stay with the 5,000, 10,000 and 20,000 lipase unit designations. The proposed upper limits for the protease and amylase content (b) (4) of label claim) are excessive.**

- **Further Discussion:**

Sponsor:

We feel that what patients actually received in the past is mimicked by dosage strengths labeled at 6,000, 12,000 and 24,000 IU rather than what they thought they received based on what the previous label claim was. We think it is more important to target the lipase enzyme because you get a wide variation of the amylase and protease levels during manufacturing.

FDA:

There was not a wide interbatch variation seen in the clinical trials.

Sponsor:

Only two batches were used in the clinical trials.

FDA:

The specifications need to be set to reflect what occurred during the clinical trials that were relied upon for demonstrating safety and efficacy of the drug product.

Sponsor:

This is a significant departure from other biologic products. We have looked at the previous 5-years of data and concluded that it would be almost impossible to set narrow limits for the amylase and protease enzymes because it would take a large number of pooled batches of the product to obtain a tight range.

FDA:

You can submit data to demonstrate your claim that it is too difficult to obtain a product with the prescribed ranges for amylase and protease consistently. You can submit a proposal to pursue that topic.

- **Question 9:** *Discussion of estimated timing for full responses to June 6, 2003 CMC deficiencies.*

The sponsor projected that it will take four to six months to characterize the drug product and make lots to target 100% potency. They are repackaging the product and collecting stability

data. It would take six months for them to respond to the Agency's request from July 9, 2003. With the addition of the August 20, 2003, request, the sponsor is concerned that the approval of the application could be delayed.

- **FDA Response:**

We need a full response to the questions we requested from you submitted to the NDA for review before we can consider approval of the application. If you have more information and need to discuss further issues, we will talk with you. If you would like to have a meeting, please share what data you have generated thus far. You need to provide at least substantial characterization data to have a productive meeting. If you need clarification, we can have a teleconference.

CONCLUSIONS:

- The following items need to be provided to the NDA:
 - Characterization of the FIP reference standards for purity and identity.
 - Separate, independent standards for each enzyme in the drug product.
 - Protease assays that are specific for each of the enzymes to be tested.
 - Well-defined enzyme substrates in all assays.
 - Assay specificities for the assay methods.
 - Drug Substance Assay validation.
 - Lipase, amylase and protease assay validations.
 - Full testing Plan
 - Complete and Revised Stability Protocol.
 - Drug Substance characterization.
 - Revised labeling.

ACTION ITEMS:

- Solvay will research what is available regarding reference standards for lipase, amylase and protease.
- Solvay will supply the requested information regarding specific enzyme assays.
- Solvay will provide the locations for the method validation data in the NDA.
- Solvay will modify the FDA program and provide improved stability graphical representations.
- Solvay will submit proposals for drug substance and drug product characterizations after having discussions.

- Solvay will reformulation to 100% of label claim with tighter ranges for amylase and protease or submit data and/or a proposal to demonstrate that it is too difficult to obtain a product in those prescribed ranges.

{See appended electronic signature page}

Signature, recorder

{See appended electronic signature page}

Signature, Chair

drafted: dm/8.26.03

revised: L.Zhou 9.2.03

initialed: A.Al-Hakim 8.27.03/M.Ysem, L.Zhou 9.2.03/M.Haber 9.4.03/E.Duffy 9.9.03

Finalized: September 9, 2003

Filename: N20725TC82503.doc

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/s/

Diane V. Moore
9/9/03 04:25:53 PM

Martin Haber
9/15/03 10:18:18 AM



NDA 20-725

Solvay Pharmaceuticals, Inc.
Attention: Karen Quinn, Ph.D.
Manager, CMC Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Dr. Quinn:

Please refer to the teleconference between representatives of your firm and the FDA on July 16, 2003. The purpose of the meeting was to request additional information to clarify the stability analyses results submitted in the July 9, 2003, submission to NDA 20-725.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Diane Moore
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE

MEETING DATE: July 16, 2003

TIME: 5:00 - 5:30 PM

LOCATION: Room 6B-45 (Parklawn)

APPLICATION: NDA 20-725; Creon[®] 5, 10, 20 Minimicrospheres (pancrelipase Delayed-Release Capsules, USP)

TYPE OF MEETING: Guidance; Biometrics

MEETING CHAIR: Dr. Wen-Jen Chen

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGICDP; HFD-180)

Diane Moore – Regulatory Health Project Manager, DGICDP (HFD-180)

Division of Biometrics II (DBII; HFD-715)

Wen-Jen Chen, Ph.D., Statistical Reviewer

EXTERNAL CONSTITUENT ATTENDEE AND TITLE:

Solvay Pharmaceuticals Inc.

Karen Quinn, Ph.D., Manager, CMC Regulatory

BACKGROUND:

On July 31, 1997, (received August 1, 1997) Solvay Pharmaceuticals submitted NDA 20-725 for Creon[®] 5, 10 and 20 Minimicrospheres (pancrelipase delayed-release capsules, USP) for treatment of adult and pediatric patients with exocrine pancreatic insufficiency. This condition is often associated with, but not limited to, cystic fibrosis, chronic pancreatitis, post-pancreatectomy, post-gastrointestinal by-pass surgery or ductal obstruction of the pancreas or common bile duct. The application was filed September 30, 1997.

On June 6, 2003, DGICDP sent Solvay Pharmaceuticals Inc. (Solvay) an information request letter requesting clinical and chemistry and manufacturing information. On July 9, 2003, Solvay submitted a response to the chemistry information requests in the Agency June 6, 2003, letter.

On July 16, 2003, Dr. Wen-Jen Chen and Diane Moore contacted Mr. George McCauley, Director, Regulatory Affairs, Chemistry, Manufacturing and Quality Control, Solvay, to request statistical clarifications on the stability analyses results received in the July 9, 2003, submission to the Creon NDA. Mr. McCauley requested we also discuss our requests with Dr. Karen Quinn, Manager, CMC, Solvay. The following information was requested through Dr. Quinn.

MEETING OBJECTIVE:

To request additional information to clarify the stability analyses results submitted in the July 9, 2003, submission.

DISCUSSION POINTS:

1. The July 9, 2003, submission contained twelve files on lipase, amylase, protease and dissolution for each strength (5,000, 10,000 and 20,000) for Creon, each containing data tables analyzed using 12S, 100s and 250s. DGICDP asked Solvay to clarify the three different sets of information for each of the twelve files. The sponsor clarified that the 12s, 100s and 250s are the package sizes for the 5,000, 10,000 and 20,000 lipase units.
2. DGICDP requests the sponsor submit the following information in reports and SAS programs for each of the twelve PDF files in the July 9, 2003, submission:
 - a. An explanation as to what was done to produce the output files for the drug product,
 - b. A clarification of the test parameters for each file (e.g., potency, dissolution or other),
 - c. The upper and lower specification limits used in the analyses,
 - d. The data batch numbers used in the analyses,
 - e. The percent confidence interval (CI) 95% one-sided CI or two sided CI used for the analyses, and
 - f. The expiration dates generated for each batch used in the analysis for each file.

CONCLUSIONS:

- Solvay will provide the following for each PDF file. (The information will be clearly labeled for linking to the associated PDF file).
 - export SAS transport file for each 12 data sets from the PDF files,
 - SAS program according to the ITT guidance (if an electronic version is not available, a PDF version will be submitted),

- an information file explaining what is in each file, and
- PDF output files for each PDF file.

ACTION ITEMS:

- Solvay will submit the requested documents to the NDA.

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Signature, recorder

Signature, Chair

Post Meeting Addendum:

On July 17, 2003, Dr. Chen and Ms. Moore called Dr. Quinn to request additional information to clarify the statistical methodology for creating the report.

- In the PDF file for Creon 10,000 Amylase file, for the 12s package size, under batch 8943012, the fitted regression lines “Y= “ for the regression analyses are missing intercept terms, only slope terms are present.
- For the output for Creon 10,000 Amylase 250s, stability analysis, the table Stability Analysis Creon 10,000 Amylase 250s, On row “C” under heading “P,” the variable is (b) (4). The slopes for the five batches should be common slope according to the preliminary slope difference test. The sponsor should use the common instead of the individual slope for all five data batches from 91625250 through 90871250.
- The predicted values listed in the submitted Creon 10,000 Amylase PDF file cannot be derived from the fitted regression lines presented in the PDF file. DGICDP requests the sponsor clarify this discrepancy.
- The DIGDCP asked the sponsor to clarify what algorithm was used to generate the PDF files submitted to the Agency in support of this NDA.

Dr. Quinn will check with their statistician regarding the accuracy of the program and datasets.

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/s/

Diane V. Moore
7/30/03 06:26:33 PM



NDA 20-725

Solvay Pharmaceuticals, Inc.
Attention: Karen Quinn, Ph.D.
Manager, CMC Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Dr. Quinn:

Please refer to the meeting between representatives of your firm and FDA on June 19, 2003. The purpose of the meeting was to discuss clinical information requested in the June 6, 2003, Agency letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Diane Moore
Regulatory Health Project Manager
Division of Gastrointestinal &
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF TELECONFERENCE

MEETING DATE: June 19, 2003

TIME: 2:00 - 2:30 PM

LOCATION: Room 17 B-43 (Parklawn)

APPLICATION: NDA 20-725; Creon[®] 5, 10, 20 Minimicrospheres (pancrelipase Delayed-Release Capsules, USP)

TYPE OF MEETING: Guidance; Clinical

MEETING CHAIR: Dr. Hugo Gallo-Torres

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGCIDP; HFD-180)

Robert L. Justice, M.D., M.S., Director,
Joyce Korvick, M.D., M.P.H., Deputy Director
Hugo Gallo-Torres, M.D., Ph.D., Gastrointestinal Medical Team Leader
Diane Moore, Regulatory Health Project Manager

Division of New Drug Chemistry II (DNDC II; HFD-820)

Eric Duffy, Ph.D., Director

EXTERNAL CONSTITUENT ATTENDEE AND TITLE:

Solvay Pharmaceuticals Inc.

Edwin Billips, Regulatory Affairs
Don Ruggirello, Director, Regulatory Affairs
Steve Caras, M.D., Director, Clinical Operations
Adam Allgood, Pharm. D., Associate Director Clinical Operations

BACKGROUND:

On July 31, 1997, (received August 1, 1997) Solvay Pharmaceuticals submitted NDA 20-725 for Creon[®] 5, 10 and 20 Minimicrospheres (pancrelipase delayed-release capsules, USP) for treatment of adult and pediatric patients with exocrine pancreatic insufficiency. This condition is often associated with, but not limited to, cystic fibrosis, chronic pancreatitis, post-pancreatectomy, post-gastrointestinal by-pass surgery or ductal obstruction of the pancreas or common bile duct. The application was filed September 30, 1997.

On June 6, 2003, DGICDP sent Solvay Pharmaceuticals Inc. (Solvay) an information request letter requesting clinical and chemistry and manufacturing information. On June 9, 2003, Solvay requested a teleconference to clarify all items in the letter.

MEETING OBJECTIVE:

To discuss clinical information requested in the June 6, 2003, Agency letter.

DISCUSSION POINTS:

Follow-up data

In the clinical section of the letter, four items are requested. The first item requests follow-up data on the patients from the randomized clinical trials submitted in support of the NDA. The Division clarified that the request is for follow-up data, especially safety data, from the three pivotal trials and the two supportive trials and any available information from any ongoing studies or references that support the two indications.

The second and third items request safety reporting from European and Canadian sales databases and safety data regarding fibrosing colonopathy. This is further safety data the Division is requesting the sponsor submit to the NDA.

Product degradation

The test article shows a loss of potency greater than (b) (4) degradation over one year. The product is manufactured at (b) (4) of the label claim. The potency of the product changes over time and degradation products increase over time, therefore, the safety and efficacy of the product at two different time points may not be comparable. Patients enrolled soon after the test batch was manufactured would get a different dose than those enrolled later. The Division is requesting enrollment dates, duration of treatment and an estimate of the dose per day for patients; and lot numbers of batches used in the clinical trials. The estimate of the dose should be based upon stability data. The estimate may be based upon two-week periods, provided there is no significant difference over this time frame. This may give the Division the means to assess the difference in potency over time for this product in terms of safety and efficacy.

The sponsor asked if they could submit average doses for patients. The Division responded that average doses may be acceptable as long as the periods of time are not long (one to two weeks at most). The Division prefers one-day increments.

The Division will send the sponsor the study numbers for the specific studies from which this information is needed. This includes the three pivotal clinical studies, one bioequivalence study and two supportive studies.

Potential review issue

Item 2 under potential review issues mentions that preliminary assessment of the data indicates that the data are incomplete for the chronic pancreatitis indication. The sponsor requested that the Division clarify this item. The Division responded that it is concerned that the "N" number of 27 for the chronic pancreatitis indication may be too small to support that indication.

CONCLUSIONS:

The Division has requested additional safety information from the three pivotal and two supportive trials for the cystic fibrosis and chronic pancreatitis indications and any available information from on-going studies.

The sponsor will submit available safety data and data on patient exposure and batch numbers from the pivotal clinical and two supportive trials to the NDA.

ACTION ITEMS:

- The sponsor will submit available follow-up data from the three pivotal trials and the two supportive trials and any available information from any ongoing studies or references that support the two indications.
- The Division will provide the study numbers for the studies from which additional batch information is needed.
- The sponsor will submit the requested patient and batch information in an expedited manner.

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/s/

Diane V. Moore
7/2/03 11:02:19 AM



NDA 20-725

Solvay Pharmaceuticals, Inc.
Attention: Karen Quinn, Ph.D.
Manager, CMC Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Dr Quinn:

Please refer to the meeting between representatives of your firm and FDA on June 13, 2003. The purpose of the meeting was to discuss the information request letter requesting clinical and chemistry and manufacturing information.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Diane Moore
Regulatory Health Project Manager
Division of Gastrointestinal &
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF TELECONFERENCE

MEETING DATE: June 13, 2003

TIME: 1:00 - 1:30 PM

LOCATION: Room 13 B-45 (Parklawn)

APPLICATION: NDA 20-725; Creon[®] 5, 10, 20 Minimicrospheres (pancrelipase Delayed-Release Capsules, USP)

TYPE OF MEETING: Guidance; Chemistry & Manufacturing (CMC)

MEETING CHAIR: Dr. Eric Duffy

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGCIDP; HFD-180)

Diane Moore – Regulatory Health Project Manager, DGICDP (HFD-180)

Division of New Drug Chemistry II (DNDC II; HFD-820)

Eric Duffy, Ph.D. – Director
Liang Zhou, Ph.D., Chemistry Team Leader
Martin Haber, Ph.D. Chemist

EXTERNAL CONSTITUENT ATTENDEE AND TITLE:

Solvay Pharmaceuticals Inc.

Karen Quinn, Ph.D., Manager, CMC Regulatory

BACKGROUND:

On July 31, 1997, (received August 1, 1997) Solvay Pharmaceuticals submitted NDA 20-725 for Creon[®] 5, 10 and 20 Minimicrospheres (pancrelipase delayed-release capsules, USP) for treatment of adult and pediatric patients with exocrine pancreatic insufficiency. This condition is often associated with, but not limited to, cystic fibrosis, chronic pancreatitis, post-pancreatectomy, post-gastrointestinal by-pass surgery or ductal obstruction of the pancreas or common bile duct. The application was filed September 30, 1997.

On June 6, 2003, DGICDP sent Solvay Pharmaceuticals Inc. (Solvay) an information request letter requesting clinical and chemistry and manufacturing information. On June 9, 2003, Solvay requested a teleconference to clarify all items in the letter, especially the first four items.

MEETING OBJECTIVE:

To discuss the information request letter requesting clinical and chemistry and manufacturing information.

DISCUSSION POINTS:

Drug Substance Specifications:

The proposed drug substance specifications are inadequate. Specifically, the acceptance specifications should be based on the characterization of the product. The lots used in the clinical trials should be specified according to the Q6B Guidance entitled "Specifications; Test Procedures and Acceptance Criteria for Biotechnological/Biological Products." Meeting specifications in the Pharmacopeia for pancreatic enzymes is inadequate, especially regarding the assay range. The proposed range for lipase activity is too broad. An upper limit needs to be set for protease and amylase activities. The overages proposed for pancreatic enzymes are too large. Because biological extracted products are complex are complex and not easily definable, standards must be improved over what the Pharmacopeia recommends.

USP Monograph Specifications

The second statement in the June 6, 2003, Agency letter states "The proposed specifications for the drug product (based on the USP monograph) are inadequate. Specifications for the drug product should include tests for identity, biological activity of different classes of enzymes, degradedants, dissolution and other relevant attributes. Establish and justify appropriate acceptance criteria." The sponsor claims to have all the items except the degradedants. The Agency reminded the sponsor that the test for identity from USP tests may not be adequate and that further data from the sponsor is needed. In addition, the other relevant attributes include specifications for impurities.

The reference to the biological activity of different classes of enzymes refers to lipase, protease, amylase and other enzymes that may be present and to their degradedants. Currently, there is nothing in the USP that addresses impurities and/or degradedants from these enzymes.

The sponsor will study the characterization that has been done and generate additional data. The sponsor will prepare specifications for the product and follow-up with a teleconference or face-to-face meeting with the Agency to discuss the issues further.

The sponsor will need to submit a pre-meeting package. The Agency will not approve specifications in a meeting, but will review the sponsor's approaches for soundness. Scientific Protein Labs (the drug substance manufacturer and DMF holder) may need to be included in the future meeting. Solvay is meeting with them.

To repeat, USP specifications set a lower limit for amylase and protease. However, both upper and lower limits are required. The proposed range is too large for lipase. The identification test is inadequate. The sponsor needs to provide characterization data, specifications with proper acceptance limits and impurity and degradation data related to drug substance (see Q6B guidance).

Overage

The proposed stability overage is not acceptable. The Agency understands that the activity of this product decreases over time. However, the purpose for having 100% potency is to have a product with an accurate potency reflected in the labeling so the physician can prescribe the proper dose. The sponsor should formulate three batches of drug product at 100% of the label claim

The sponsor asked if a small overage could be acceptable. The Division responded that the sponsor could propose an amount. The Agency reminded the sponsor that they need to aim to have close to 100% potency at release. In general, any in-process overage should be justified due to manufacturing losses. The loss/degradation could be a formulation, packaging or storage issue.

Analysis of Stability Data

In the fourth item in the June 6, 2003, Agency letter, the sponsor was requested to "provide a complete analysis of the stability data, including trend data for all test results. Provide the true potency of the clinical trial batches at the time of the clinical trials." The sponsor proposed to analyze the lots they used for expiry dating. The Agency requested regression analyses for the enzyme assays and for dissolution. Proper acceptance limits for the specifications are needed to analyze statistically the stability of the material. The sponsor noted that the raw data was submitted to the NDA in paper and electronic copies. In addition, statistical analysis files were included in electronic form.

True potency of clinical batches in the pivotal clinical trials

The Agency will provide the trial numbers for the requested clinical batch information. (Note added in proof: A list of 25 clinical trial numbers and relevant batch lot numbers was given in the original 1997 submission, Chemistry Vol. 1.2, pp. 62-66. The clinical reviewer should confirm that this information includes all relevant trials). The expiry period will be based on stability lots, not clinical trial lots.

Residual Impurities

The sponsor understands the request for specifications and limits on residual [REDACTED] (b) (4) [REDACTED] content. There was no discussion on this topic.

List of tests and certificates of analysis for all excipients

The sponsor understands the request for a list of tests and representative certificates of analysis for all excipients. There was no discussion on this topic.

December 16, 2002, Major Amendment

The Agency inquired whether the stability data submitted in the December 16, 2002, amendment is current. The sponsor said that the stability data was current up to August 2002. The sponsor can provide updates to the stability data beyond August 2002. The Agency reminded the sponsor that additional information submitted to the NDA late in the review cycle may not be reviewed for lack of time. The sponsor said they could submit the data next week.

The BSE certification and package issues are the same as in the December amendment that replaced the CMC section of the NDA for container closure drug substance source information. The Agency noted that the BSE statement submitted in the December 16, 2002, amendment may not be adequate for the current guidelines. The sponsor suggested the FDA refer to the DMFs for the capsules. (This may require further clarification later).

CONCLUSIONS:

Drug Substance Specifications:

The proposed drug substance specifications are inadequate. Meeting specifications in the Pharmacopeia for pancreatic enzymes is inadequate, especially regarding the assay range. The proposed range is too broad.

USP Monograph Specifications

The proposed specifications for the drug product (based on the USP monograph) are inadequate. The sponsor will examine the characterization that has been done and generate additional data. The sponsor will prepare specifications for the product.

Overage

The proposed stability overage is not acceptable. The sponsor should formulate three batches of drug product at 100%. The capsules need to have 100% potency at release. The overage should be due to manufacturing losses. The sponsor could propose an amount of overage with supporting data.

Analysis of Stability Data

The sponsor proposed to analyze the lots they used for expiry dating. The Agency requested regression analyses for the assay and for dissolution.

True potency of clinical batches in the pivotal clinical trials

The Agency will provide the trial numbers for needed clinical batch information.

Stability Data

The sponsor will provide updates to the stability data

The Agency noted that the BSE statement submitted in the December 16, 2002, amendment may not be adequate for the current guidelines.

ACTION ITEMS:

- The sponsor will meet with the Agency to further discuss the specifications for the drug product issues. Scientific Protein Labs may need to be included in the future meeting.
- The sponsor will prepare specifications for the product. The sponsor will analyze the lots they used for expiry dating. The Agency requested regression analyses for the assay and for dissolution.
- The Agency will provide the trial numbers for needed clinical batch information.
- The sponsor could propose an amount of overage with supporting data.
- The sponsor will provide updates to the stability data to the NDA.

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/s/

Diane V. Moore
6/30/03 01:20:16 PM



FILING REVIEW LETTER

NDA 20-725

Solvay Pharmaceuticals
Attention: Edwin Billips
Regulatory Affairs Manager
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Billips:

Please refer to your July 31, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Creon[®] (pancrelipase delayed-release capsules).

We also refer to your submission dated December 16, 2002.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on September 30, 1997, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. Based on safety information for fibrosing colonopathy, the amount of enzyme tested for the cystic fibrosis indication may be higher than the maximum recommended Lipase Units/kg.
2. Preliminary assessment of the data indicates that the data are incomplete for the chronic pancreatitis indication. The clinical study submitted in support of the chronic pancreatitis indication may not be adequately powered to support efficacy for this indication. In addition, the doses of enzymes used in the study may not be adequate to demonstrate efficacy for this indication.
3. The potency of the drug product may not be consistent throughout the proposed expiration period for the product.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

Clinical

1. Follow-up data on the patients from the randomized clinical trials submitted in support of the NDA.
2. Spontaneous safety reporting from the European and Canadian sales databases in support of the safety of the drug.
3. Safety data establishing that the product does not result in fibrosing colonopathy when used at the dosages studied in the clinical trials.
4. Due to our concerns regarding product degradation, additional clinical information is needed. For each patient, provide the date of enrollment, the duration of treatment, and the dose administered per day per protocol for all clinical trials. Based upon stability data, provide an estimate of actual enzyme administered (lipase, protease, amylase) to each patient in the clinical trials including patients in the clinical pharmacology study KREO.629. These data will provide the corrected dose due to batch degradation at the time of treatment.

Chemistry, Manufacturing and Quality Control

1. The DMF for the drug substance and the proposed drug substance specifications are inadequate. Propose appropriate acceptance specifications for the drug substance. Refer to the ICH guidance Q6B entitled "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products."
2. The proposed specifications for the drug product (based on the USP monograph) are inadequate. Specifications for the drug product should include tests for identity, biological activity of different classes of enzymes, degradants, dissolution and other relevant attributes. Establish and justify appropriate acceptance criteria.
3. The use of large stability overages for the potency is not acceptable. The drug product should be formulated to contain 100% of label claim at release. Establish upper limits and tight ranges on the content of all enzyme activities. Re-formulate three batches at 100% of label claim, and collect release and stability data. Provide batch records from at least one batch.
4. Provide a complete analysis of the stability data, including trend data for all test results. Provide the true potency of the clinical trial batches at the time of the clinical trials. If the stability is inadequate, a shortened expiry period may be required.
5. Establish specifications and limits on the residual (b) (4) content based on your batch test data (refer to ICH Q3C-guidance entitled "Impurities: Residual Solvents" for maximum allowable daily exposures).

6. Provide a list of tests and representative certificates of analysis for all excipients. Provide a copy of the European Pharmacopoeia (Ph. Eur.) monograph for dibutyl phthalate.
7. Verify that all information provided in the NDA for all components of the drug product are current.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
6/6/03 11:45:43 AM
Signing for Julieann DuBeau, CPMS.



NDA 20-725
Solvay Pharmaceuticals
Attention: Edwin Billips
Regulatory Affairs Manager
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Billips:

Please refer to your July 31, 1997, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CREON[®] Minimicrospheres[®] (pancrelipase delayed-release capsules, USP)

We also refer to the Agency letter dated April 9, 2003, informing you that the Application Integrity Policy (AIP) was revoked for Solvay Pharmaceuticals, Inc.

Review of the Creon NDA was suspended during the time the AIP was in effect. The time frame for review restarted as of the date the AIP was revoked. Therefore, the due date for this application is October 9, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-725

Page 2

If you have any questions, call Diane Moore, Regulatory Health Project Manager, at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.

Director

Division of Gastrointestinal & Coagulation Drug
Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

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/s/

Robert Justice
5/31/03 12:24:40 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: May 30, 2003

To: Edwin Billups	From: Diane Moore
Company: Solvay Pharmaceuticals	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: 770-578-5864	Fax number: (301) 443-9285
Phone number: (770) 578-5685	Phone number: (301) 827-7476

Subject: NDA 20-725 Statistical information request

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-7310. Thank you.

Attachment

INFORMATION REQUEST

Date: May 29, 2003

NDA: 21-725

Sponsor: Solvay Pharmaceuticals

Drug: Creon[®] Minimicrospheres (Pancrelipase Delayed-Release Capsules, USP)

Indication: Treatment of adult and pediatric patients with exocrine pancreatic insufficiency.

Mr. Billips,

We are reviewing the statistical section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the following information for the three Studies CR200.0126 (Protocol S2233101), CR200.0143 (Protocol S2233102), and CR200.0124 (Protocol 223201):

Data for both Intent-to-Treat (for efficacy analysis) and Total-Patient (for safety analysis) populations in electronic format consistent with the guidance, *Regulatory Submissions in Electronic Format; General Considerations*. We suggest you include the following variables:

- Study number (or Protocol number);
- Investigator or Center code;
- Patient number/name;
- Treatment name;
- Intent-to-Treat population (yes or no);
- Total-Patient population (yes or no);
- Gender;
- Age;
- Race;
- Coefficient of Fat Absorption (%) at Baseline (ie. *open-label creon phase for Studies CR200.0126 and CR200.0143; single-blind placebo phase for Study CR200.0124*);
- Coefficient of Fat Absorption (%) at double blind phase;
- Fat Intake (g/24 hrs) at Baseline;
- Fat Intake (g/24 hrs) at double blind phase;
- Fecal Fat Excretion (g/24 hrs) at Baseline;
- Fecal Fat Excretion (g/24 hrs) at double blind phase;
- Stool Frequency at Baseline;
- Stool Frequency at double blind phase;
- Stool Consistency at Baseline;
- Stool Consistency at double blind phase;

Clinical Global Improvement rated by physician for *Studies CR200.0126 and CR200.0143*;
Clinical Global Impression of Disease Symptoms rated by physicians at Visits 3 and 4 for
Study CR200.0124;
Clinical Global Impression of Disease Symptoms rated by patients at Visits 3 and 4 for
Study CR200.0124;

2. For the two Studies *CR200.0126 and CR200.0143*, please perform the statistical efficacy analyses stated in the subsection of *6.33 Efficacy Parameters* on page 32 of Volume 73 to generate Table 12, Table 13, Table 14, Table 15, Table 16, and Table 17.

For Study *CR200.0124*, perform the statistical efficacy analyses stated in the subsection of *6.1.2 Efficacy Analysis* on page 36 of Volume 83 to generate Table 11, Table 12, Table 13, Table 14, Table 15, and Table 16.

To the data set described in Item 1. above, please add additional variables, as needed, for the above analyses. Modify the programs to be able to input data from the data set described in Item 1.

If you have any questions, call Diane Moore, Regulatory Health Project Manager at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation Drug
Products (HFD-180)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Diane V. Moore
6/2/03 09:14:02 AM
CSO
For Julieann DuBeau, MSN, RN

Diane V. Moore
6/2/03 09:16:55 AM
CSO
For Julieann DuBeau, MSN, RN



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Division of New Drug Chemistry II

Memorandum

Date: May 9, 2003

From: Martin Haber, Ph.D., Review Chemist, HFD-510

Through: Liang Zhou, Ph.D., Chemistry Team Leader, HFD-180
Eric Duffy, Ph.D., Director, Division of New Drug Chemistry II

Subject: NDA Filing Review

To: NDA 20-725

Background:

On July 31, 1997 Solvay Pharmaceuticals submitted NDA 20-725 for Creon 5, 10 and 20 Minimicrospheres (pancrelipase delayed-release capsules, USP). However, the sponsor was placed under the Application Integrity Policy (AIP) on September 24, 1997 and review of the NDA was suspended. The NDA was filed September 30, 1997. The Agency revoked the AIP status for Solvay on April 9, 2003.

In the meantime, the Agency has prepared a draft Guidance for Industry on Exocrine Pancreatic Insufficiency Drug Products – New Drug Application Requirements that is nearing finalization. In addition, a Federal Register Notice of a Final Rule will be published soon to notify the public that NDAs will be required within three years for all pancreatic enzyme products which are now being marketed as dietary supplements.

Chemistry Issues/Information Requests:

Drug substance information for this NDA is provided in DMF 9649. An initial filing review of the DMF found that it would normally be considered inadequate for filing from a chemistry viewpoint according to current standards. The major deficiencies in the DMF were:

1. The holder should provide characterization data for the drug substance based on ICH Guideline Q6B by appropriate chemical, physical and biological testing. Batch to batch consistency with respect to chemical identity and biological activity of different classes of enzymes including specific activity and purity level should be demonstrated. Identity may be demonstrated by fingerprinting analysis, using but not limited to the following methods for separation of the complex mixture of proteins: DEAE, CM cellulose, reverse phase or other chromatography, SDS-PAGE, 2-D Gels, and IEF. Similar methods should also be used to determine chemical purity. New analytical technology should be used when appropriate.
2. The proposed drug substance specifications (based on the USP monograph) are inadequate. Based on characterization data on your hog pancreas preparation, more appropriate specifications for the drug substance based on ICH Guideline Q6B should be proposed. Specifications should include tests for identity, biological activity of different classes of enzymes, purity, and other relevant attributes. Appropriate acceptance criteria (e.g., limits and ranges) for all relevant attributes should be established and justified based on release and stability data.
3. The use of large stability overages for the drug substance potency (e.g., as per the (b) (4) % acceptance criteria for lipase activity given in the USP) in order to extend the shelf life is not acceptable. The drug substance should contain 100% of label claim at release. The label claim should be adjusted to reflect the measured potency. Also, currently only lower limits are proposed for protease and amylase activities. Upper limits with appropriate ranges on the content of all enzyme activities should be established and justified based on batch data. Historical batch data for all measured potencies should be provided in tabular form.
4. Viral safety evaluation according to ICH guidance Q5A that has begun should be completed. Thorough evaluation and characterization/screening of the starting material (hog pancreas) should be done to identify which, if any, viral contaminants are likely to be present. The validation study for viral clearance is considered a safety issue for NDA review.

The following comments are not as serious issues but should also be sent to the DMF holder as issues identified during the initial filing review:

5. The DMF needs a complete update as it has been partly revised many times and information is scattered in several places.
6. Regarding the proposed protease assay, the holder should provide data

demonstrating individual specificity for [REDACTED] (b) (4)

[REDACTED] The use of purified enzymes for reference is recommended. If specificity cannot be demonstrated, other assay methods may be required.

7. The acceptance limit for residual [REDACTED] (b) (4) should be tightened based on your batch test data (refer to ICH Q3C guidelines for maximum allowable daily intake).
8. The holder should provide stability data at reduced temperatures since the stability at 25°C appears to be not adequate. If the stability is not adequate, restrictions in shelf life may be required. In addition, the holder should provide a trend analysis for the stability of enzyme activities other than only the lipase.
9. The holder should provide a compilation of what is known in the scientific literature about the enzyme components of the mammalian pancreas and specifically about hog pancreas components. Information regarding the properties of the purified enzyme components should also be provided.

Drug product information for NDA 20-725 is provided by the NDA sponsor, Solvay, and was completely updated on December 16, 2002. Major CMC issues include:

1. The DMF for drug substance and the proposed drug substance specifications are inadequate. Appropriate acceptance specifications for the drug substance based on ICH Guideline Q6B should be proposed.
2. The proposed specifications for the drug product (based on the USP monograph) are inadequate. Specifications for the drug product should include tests for identity, biological activity of different classes of enzymes, degradants, dissolution and other relevant attributes. Appropriate acceptance criteria should be established and justified.
3. The use of large stability overages for the potency is not acceptable. The drug product should be formulated to contain 100% of label claim at release. Upper limits and tight ranges on the content of all enzyme activities should be established. The sponsor needs to re-formulate three (pilot scale) batches at 100% of label claim, and collect release and stability data.
4. A complete analysis of the stability data should be provided, including trend data for all test results. The true potency of the clinical trial batches at the time of the clinical trials should be provided. If the stability is inadequate, a shortened expiry period may be required.

5. Specifications and limits on the residual (b) (4) content should be established based on your batch test data (refer to ICH Q3C-guidance).

Conclusions and Recommendations:

From a chemistry viewpoint, this NDA would normally be considered as not fileable as it does not contain sufficient information for a substantive review based on current chemistry standards. Since this NDA has already been filed, other regulatory options should be explored in order to expedite successful review of the application.

The drug substance is an extremely crude natural product material, derived from hog pancreas. There is no characterization data available. The proposed specifications for drug substance are inadequate. Normally, drug product specifications are proposed based on drug substance specifications. Until adequate drug substance specifications are established, drug product specifications cannot be finalized.

Since this application was originally submitted and filed in 1997, numerous ICH Guidelines (e.g., Q1A, Q2A, Q2B, Q3C, Q5A, Q5C and Q6B) have been established. In addition, specific chemistry information relevant to pancreatic enzyme products is given in the draft Pancreatic Drug Products Guidance.

The product has historically been formulated with large stability overages or with only a lower limit on the enzyme activity. The true content of the clinical trial batches may not be known or able to be discovered. This may effect the clinical evaluation by making the data invalid or uninterpretable.

The sponsor needs to re-formulate three batches at 100% of label claim, and collect release and stability data. The Pancreatic Drug Products Guidance recommends at least a year of stability data to be submitted with the NDA.

It is estimated that the sponsors will require more than one year to obtain the needed information, starting with characterization data. Therefore, if this NDA is filed as a priority application, it will not be able to be approved from a chemistry viewpoint.

Orig. NDA 20-725
cc: HFD-180/Division file/L.Zhou/M.Ysern/D.Moore
M.Haber/M.Gautam-Basak/D-G.Wu/E.Duffy

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/s/

Martin Haber
5/9/03 04:40:16 PM
CHEMIST

Liang Zhou
5/9/03 04:46:01 PM
CHEMIST

Eric Duffy
5/13/03 01:10:18 PM
CHEMIST

MEMORANDUM OF MEETING

MEETING DATE: April 28, 2003

TIME: 3:30 - 4:30 PM

LOCATION: Room 6 B-45 (Parklawn)

APPLICATION: NDA 20-725; Creon[®] 5, 10, 20 Minimicrospheres (pancrelipase Delayed-Release Capsules, USP)

TYPE OF MEETING: Team Meeting

MEETING CHAIR: Dr. Robert Justice

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGCIDP; HFD-180)

Robert L. Justice, M.D., M.S., Director
Joyce Korvick, M.D., M.P.H., Deputy Director
Hugo Gallo-Torres, M.D., Ph.D., Medical Team Leader, Gastrointestinal Drug Products
Diane Moore – Regulatory Health Project Manager, DGCIDP (HFD-180)
Jasti Choudary, B.V.Sc., Ph.D. – Supervisory, Pharmacologist
David Joseph, Ph.D. – Pharmacologist

Division of New Drug Chemistry II (DNDC II; HFD-820)

Eric Duffy, Ph.D. – Director
Liang Zhou, Ph.D., Chemistry Team Leader
Maria Ysern, M.S. – Chemist
Martin Haber, Ph.D. Chemist

Office of Clinical Pharmacology and Biopharmaceutics (OCPB; HFD-870)

Suresh Doddapaneni, Ph.D. - Biopharmaceutics Team Leader
Sue-Chi Lee, Ph.D. - Biopharmaceutics Reviewer

Division of Biometrics II (DBII)

Tom Permutt, Ph.D. - Team Leader
Wen-Jen Chen, Ph.D. - Statistician

BACKGROUND:

On July 31, 1997, (received August 1, 1997) Solvay Pharmaceuticals submitted NDA 20-725 for Creon[®] 5, 10 and 20 Minimicrospheres (pancrelipase delayed-release capsules, USP) for treatment of adult and pediatric patients with exocrine pancreatic insufficiency. This condition is often associated with, but not limited to, cystic fibrosis, chronic pancreatitis, post-pancreatectomy, post-gastrointestinal by-pass surgery or ductal obstruction of the pancreas or common bile duct. The application was filed September 30, 1997. The sponsor was placed under the Application Integrity Policy (AIP) on September 24, 1997, and review of the Creon NDA was suspended.

On October 9, 1997, the Division sent the sponsor a letter requesting several items including English translations of foreign labeling for Creon, a list of names of manufacturing facilities, documentation of assay validation for the bioavailability study, *in vitro* dissolution profiles on 12 dosage units of the highest dosage strength of Creon and an explanation for why the number of patients randomized in each of the three pivotal studies is less than the number planned in the study protocols. The sponsor submitted several amendments to the NDA between December 18, 1997 and December 16, 2002.

On March 22, 2002, the sponsor submitted a request that review of the NDA be resumed for the following reasons: (1) a third-party validity assessment audit of the NDA concluded that no integrity issues exist in this application; (2) there is a clear medical need to resume review of the application because of efficacy and safety concerns regarding other pancreatic enzyme preparations which are being dispensed as a substitute for Creon; and (3) the only approved pancreatic enzyme product (Cotazym) was discontinued in June 2002.

In a letter dated November 21, 2002, the Division informed the sponsor that, after considering their request, the Division had concluded that an exception to the AIP was not warranted, and that review of the NDA would not resume until AIP status is revoked.

The Agency revoked the AIP status for Solvay on April 9, 2003.

MEETING OBJECTIVE:

To discuss the review class for the Creon NDA and whether a priority review and advisory committee meeting are warranted.

DISCUSSION POINTS:

Drug Classification:

The active moiety is not a new molecular entity. The previously-approved drug Cotazym (NDA 20-580) also consists of pancreatic enzymes. There are many currently-marketed products containing pancreatic enzymes that are not approved NDA products. They are pre-1938 products marketed as dietary supplements. This product under consideration (Creon) is also currently being marketed as a dietary supplement. This product should be classified as a "Type 7" (Drug already marketed but without an approved NDA). It also should be classified as a "Type 3" – New formulation.

Priority Review Issue:

- According to the Priority Review Policy in MAPP 6020.3, a determination for priority classification is made based on an estimate of its therapeutic preventive or diagnostic value. To be a priority review, the drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for example (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation.
- There is only one approved NDA for pancreatic enzyme product. Cotazym (NDA 20-580) is an immediate release product. Marketing of Cotazym was discontinued by the sponsor in June 2002.
- The draft guidance for pancreatic enzymes is nearing finalization. A Federal Registry Notice will be published soon to notify the public that NDAs will be required within three years of the FR Notice for all pancreatic enzyme products. After the 3-year window, products without an approved NDA will be considered misbranded.
- Creon is a different formulation from Cotazym in that it is enteric-coated for delayed release into the intestine.
- Because the sponsor did not carry out active-control comparison studies, the data submitted to the NDA are not designed to demonstrate a significant improvement compared to specific marketed products. However, this is the first delayed release product to submit clinical data to an NDA application for these indications. Because this NDA application will be reviewed in light of current Division policy regarding pancreatic enzymes and the draft Pancreatic Enzyme Guidance is soon to be released, it may be appropriate to discuss policy issues

regarding this pancreatic enzyme product at an Advisory Committee Meeting. This decision will be made at a later time.

- Two indications associated with pancreatic insufficiency are being sought: treatment of cystic fibrosis and treatment of chronic pancreatitis. In support of the first indication, the sponsor has submitted results of two pivotal studies and these can be reviewed. There is only one study (which may not be adequate) submitted in support of the chronic pancreatitis indication. The sponsor tested an amount of enzyme that is higher than the maximum allotted Lipase units/kg recommended for the cystic fibrosis indication based on the fibrosing colonopathy issue. On the other hand, for chronic pancreatitis, the sponsor tested amounts of enzyme that might be insufficient to adequately treat this condition.

Chemistry issues

1. Drug Substance:

- The DMF for drug substance, DMF 9649, was last reviewed in 1992. It was revised many times and needs a complete update.
- The DMF does not contain characterization data for the drug substance. As expected of what is known of pancreatic exocrine secretions, the enzyme components consist of about four proteases, three lipases and an alpha-amylase. The DMF does not contain any purity data on the product. The product is extremely impure. The original source is the hog pancreas. The DMF does not contain data to formulate specifications. The current USP monograph for pancreatic enzymes is obsolete.
- The DMF holder has added some data to the DMF recently on viral clearance. These data have not been reviewed, but it appears that clearance is less than the amount normally requested for protein products
- The information in the DMF is insufficient to support the drug substance submitted to this NDA. The inadequacy of the CMC data is considered a filing issue by the chemistry team.

2. Drug Product:

- The drug product is a complex drug product (enteric coated pellets).
- The NDA lists the potency coverage as follows: Lipase: (b) (4), of label claim; Amylase, Protease: NLT (b) (4). This coverage for these products is unacceptable as discussed in the draft Pancreatic Enzyme Guidance.
- Without adequate drug substance data to set specifications, it is impossible to set drug product specifications.

- If the sponsor is required to make substantial changes to the drug product in order to conform to the Pancreatic Enzyme Guidance for potency, the resulting product could be a different product from the product used in the clinical trials.

3. Drug Classification

- The classification of the NDA should be a "7" because the product is an unapproved marketed product. Creon is not a new molecular entity, however, it is a new formulation (delayed release). Therefore, it should also be classified as a "Type 3."

CONCLUSIONS:

1. The Creon NDA should be listed as a type "3, 7" drug.
2. The Pancreatic Enzyme Guidance will be posted in the near future. Along with the release of the Guidance, a Federal Register Notice will be posted to inform the public that an NDA will be required for these products three years after the posting of the FR notice. The products on the market that do not submit NDA applications will be considered misbranded and taken off the market. That leaves only one approved NDA product and that product was discontinued in June 2002. The Creon product would be the first delayed release pancreatic enzyme NDA. In light of the fact that no currently marketed delayed release pancreatic enzyme product has submitted clinical data to support the safety and efficacy of the product for cystic fibrosis or chronic pancreatitis, if the Creon NDA contained data that demonstrated safety and efficacy for either indication, it would be evidence of increased effectiveness in treatment, prevention, or diagnosis of disease over existing marketed products.
3. Consistent with the above considerations, a newly approved product is expected to be of a better quality and allow more consistent administration of the amount of enzymes to assure safety and efficacy for the indications under consideration. At this meeting, the Medical Team Leader, Dr. Hugo Gallo-Torres, recommended that the Creon NDA be reviewed as a priority submission. The Division Director, Dr. Robert Justice, agreed with this recommendation. Therefore, the division decided that NDA 20-725 will be a priority review
4. It is very unlikely that this product will meet the quality requirements needed to meet the medical concerns discussed in previous policy meetings. From a CMC viewpoint (according to ICH guidelines and Federal Register regulations) this application is clearly inadequate and should not be filed at this point.
5. The Creon NDA should be discussed at an Advisory Committee Meeting to debate the complex issues regarding this product in light of current policies to be included in the draft Pancreatic Enzyme Guidance. This decision will be made at some time in the future.

ACTION ITEMS:

Diane Moore will determine the PDUFA user fee goal date for this product.

{See appended electronic signature page}

{See appended electronic signature page}

Signature, recorder

Signature, Chair

Post Meeting Addendum:

Review of the Creon application was restarted on April 9, 2003. This is a priority review. Therefore, the application has a six-month PDUFA goal date of October 9, 2003.

drafted: dm/4.29.03

revised: H.Gallo-Torres 4.29.03/M.Haber 4.30.03/L.Zhou 5/2/03/S.Lee 5.14.03

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J.Choudary 5.4.03/S.Lee 5.14.03/W.Chen/T.Permutt 5.15.03/S.Doddapaneni

5.16.03/E.Duffy, J.Korvick 5.19.03, 5.27.03

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/s/

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