

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-725

CHEMISTRY REVIEW(S)

From: Ennan Guan, M.D./Ph.D.
To: NDA: 20725, Response to Approvable Letter Dated 16 August 2007
Through: Barry Cherney, Ph.D. Deputy Director, CDER/OPS/OBP/DTP, HFM541
Product: Pancrelipase Delayed-Release Capsules
Sponsor: Creon (Drug substance manufactured by Solvay)
Final Date: March 20, 2009
Draft: November 20, 2008

Recommendation and Summary Based for Approval from a Viral Safety Perspective

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of NDA 20725 for Creon manufactured by Solvay Pharmaceuticals from a viral safety perspective. The data submitted in this response to our CR letter and shows that Solvay has addressed all the viral issues that were identified in that letter. The application showed that Solvay's manufacturing process is relatively robust and is capable of providing (b) (4) logs inactivation of enveloped viruses but has a limited capacity to inactivate non-enveloped viruses. Given that the raw material used in production of the drug substance is derived from porcine pancreatic tissue and contaminating gastro-intestinal tissue that has been shown to contain adventitious viruses that are not completely inactivated by the process, an evaluation was performed to assess the risk to patient safety. This assessment identified viral species that could potentially transmit an infectious disease. However, because these products have a long history of use and have not been shown to transmit infectious disease, the risk is view as theoretical rather than actual. Nevertheless, there is a lack of compelling data indicating that the risk from adventitious viruses is insignificant. Therefore, additional controls (specifications and action limits) have been put in place by the applicant to monitor certain zoonotic viruses and viruses that pose a risk due to the potential to change species tropism. It is important to note that not all assays used for the virological testing of drug substance are sufficiently sensitive to fully mitigate the risk to product quality nor was the viral surveillance program adequately described to provide a high level of assurance that emerging viral threats were appropriately monitored and controlled. The sponsor has however, agreed to a number of post-marketing commitments to ensure that the manufacturing process is well controlled regarding the risk associated with adventitious viruses. The draft post-marketing commitments are as follows:

Post-marketing Commitments for Viral Safety Control

1. 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. The final report and changes to Solvay's control strategy will be submitted to the Agency by [INSERT DATE].
2. Solvay commits to continue developing sensitive qPCR assays for drug substance testing that provide adequate assurance that process capability for the inactivation of non-enveloped viruses is not exceeded. Assays will be revised and assay validation data, together with new action limits, will be submitted to the Agency by [INSERT DATE].
3. Solvay commits to develop and implement specifications for infectious porcine circoviruses (PCV) 1 and 2 in the final product. The proposed specifications, including relevant method validation, will be submitted to the Agency by [INSERT DATE]. The final specifications will be developed and implemented by [INSERT DATE].
4. 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. The final risk assessment and control strategy will be submitted to the Agency by [INSERT DATE].
5. 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." The revised acceptance criteria will be submitted to the Agency by [INSERT DATE].
6. 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. The final plans will be submitted to the Agency by [INSERT DATE].
7. Solvay commits to assess the risk to product quality due to the potential infection of swineherds with parasites. The final risk assessment and control strategy will be submitted to the Agency by [INSERT DATE].

8. Solvay commits to provide a detailed description of its plans for preventing cross-contamination with material from other species, particularly with ruminant tissues. The final plans will be submitted to the Agency by [INSERT DATE].

We recommend approving this NDA based on the current information for viral safety control and post-marketing commitments to provide additional information to assure with a high degree of confidence that the manufacturing process will produce a product that is safe and effective.

I. Background

In the Creon NDA 20-725 approvable letter dated 16 August 2007, the FDA requested additional viral safety information. In addition to the complete response to additional information request, Solvay also updated viral testing for the drug substance.

II. FDA Letter Comments and Solvay Response

FDA Letter comments

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 viral load.

Solvay Response

A type A meeting between FDA and Creon (Solvay's representatives also in the meeting) was held on 17 January 2008. Solvay proposed in the briefing package 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. The FDA responded to Solvay's proposal with the following comments:

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.

Solvay provides additional supportive information on selection of test viruses in the subsequent amendment submission as below.

Rationale For Not Selecting Influenza A

Influenza viruses in swine replicated exclusively in superficial cells of the respiratory tract and preferentially binds to sialyoligosaccharides containing terminal N-acetyl sialic acid linked to galactose by an alpha 2, 6-linkage, which is expressed only by respiratory tract epithelial cell thus limiting more systemic spread but facilitating accumulation of virus in the respiratory tract for transmission by aerosols. No viremia can be demonstrated for swine influenza viruses. The absence of H3N1 in the sera experimentally (intratracheally) infected pigs was observed but virus was found in BALF (brabronchoalveolar lavage fluid) (6.3 to 7.6 logs/ml) and nasal swabs (3 to 5.8 log/ml). (Lekcharensuk et al, Emerging Infectious Diseases, Vol. 12, No. 5, May 2006)

Although influenza A virus is considered as a virus with zoonotic potential, the probability of detecting influenza virus in pancreatic or gastro intestinal material is very low due to the known tissue tropism for respiratory tract epithelial cells. Considering the hygienic controls implemented in the raw material handling as described previously, a contamination of pancreatic tissue with bronchial or nasal fluids or with lung tissue is also highly unlikely to contribute to a significant viral load that can be measured. These considerations are also supported with information of enveloped viral loads that indicated negative results for swine influenza A genomic equivalents in pancreatic samples. Solvay has demonstrated that the manufacturing process has sufficient capacity to inactivate low level viral contaminations in that they have shown that the following enveloped viruses are inactivated at: (b) (4) logs for PsRV; (b) (4) logs for BVDV; (b) (4) logs for XMuV (b) (4); and (b) (4) logs for IBRV (b) (4)

I concluded that it is acceptable that Solvay does not select influenza A for a virus load study and that an in-process specification for control of the influenza A virus may not necessary.

Rationale For Not to Select Vesicular Stomatitis Virus (VSV)

VSV is a zoonotic virus. Humans are primarily infected via the respiratory tract, conjunctiva and through skin abrasions. Symptoms in human disease resembles influenza with sporadic occurrence of vesicles on the mouth and hands, diarrhea and vomiting. Howerth et al (J Vet Diagn Invest 9: 136-142, 1997) reported that investigations in domestic pigs inoculated by various routes with VSV New Jersey serotype showed viral shedding primarily via the tonsil of soft palate, regardless of route of inoculation but virus was never isolated from blood from pigs tested in this study. Since VSV causes important economics losses, it has been subjected to rigid eradication and surveillance

measures in Europe and in the US for many years. In most parts of Europe, the disease has never been reported and single outbreak was kept under control in France in 1983. In the US, the latest epizootic in which to the great extent horses and cattle were affected, started in 2004 and persisted restricted to certain areas. There was with no report case in swine between 2005 and 2007.

It is acceptable that VSV is selected for the enveloped viral load study due to the primary site of replication and shedding for this virus is not associated with the pancreatic tissue or tissues likely to contaminate the source material. It is also noteworthy that the veterinary surveillance program should be adequate to monitor herd status preventing significant viral loads from entering the process stream. These considerations are also supported with information of enveloped viral loads that indicated negative results for VSV genomic equivalents in pancreatic samples

Rationale To Select Porcine Cytomegalovirus (PCMV)

PCMV is considered as a non zoonotic but a relevant virus as well as a substitute for other herpesviruses for example, PsRV and the porcine lymphotropic herpesviruses. Although PsRV is rarely zoonotic and then only after inoculation following a traumatic event. PsRV was used in the spiking study to represent herpesviridae for Solvay's manufacturing process. It is not convincing to select PsRV for assessment of initial viral load since PsRV is controlled in most herds and the predominant replicate sites for PsRV are oropharyngeal, and center nerve system. PCMV is found in the tissues throughout the body, exists in most, if not all pig population. Serology carried out in the UK indicates that over 90% of herds have been exposed to infection with PCMV.

It is acceptable to select PCMV to assess the ability of process to effectively control of enveloped viruses in the starting material. It is a good substitute since PsRV and PCMV belong to a same family with similar physio-chemical resistant profiles. Solvay has selected PsRV in the viral spiking studies and has shown that the manufacturing process is able to inactivate ^{(b) (4)} logs for PsRV.

Rationale To Select Transmissible Gastroenteritis Virus (TGEV)

TGEV belongs to the family coronaviridae and widely distributed in swine herds worldwide and causes severe diarrhea in young pigs (2 wk of age). Pigs that recover from TGEV develop immunity to subsequent challenge. Although this virus is not considered as a zoonotic potential pathogen TGEV replicates in the gastro-intestinal tract sheds with feces in large amounts. As shown in Table 2, detection of 50 samples for the initial TGEV load, 9 out 50 samples were detected as positive at low level, near the detection limit ^{(b) (4)} g.e./g pancrelipase. Although TGEV is widely distributed in pigs, the viral load at maximal of ^{(b) (4)} logs is much less than that of PPV or PCV at ^{(b) (4)} logs per gram of

DS. Since only adult pigs are slaughtered and low level of TGEV in adult pigs may indicate development of immunity to TGEV to be able to neutralize the virus. However, TGEV is a good marker to assess secondary contamination; TGEV may enter the process due to secondary contamination of the pancreas glands with contaminating gastro-intestinal tissue associated with the glands. Thus, it may be a good marker for assessing the level of contamination of the pancreatic glands with gastro-intestinal tissues. Additionally due to the oral administration of this product, there is a heightened concern regarding viruses that can infect through the gastro-intestinal route.

It is acceptable to use TGEV for initial enveloped viral load study.

The results are provided in this Class II Complete Response as described below.

A. Determination of The Initial Viral Load For Enveloped Viruses

A total of fifty batches which are representative for Solvay's commercial production was taken directly from the process were investigated for the content of pCMV and TGEV. Selected batches represents all countries from which pancreas glands are currently sourced.

France	2 samples
Germany	9 samples
Portugal	10 samples
Spain	16 samples
The Netherlands	6 samples
USA	7 samples

Positive PCR results for TGEV (near the detection limit ^{(b) (4)} mg pep) were observed in 5/10 samples from Portugal, 1/16 samples from Spain, and 3/7 samples from the USA.

Initial virus load was determined by Q-PCR method from the early starting material, homogenized pancreas tissue in ^{(b) (4)} RNA or DNA was extracted from starting material and subjected to real time PCR using Tagman technology. In the case of TGEV, reverse transcription was performed prior to PCR. Each sample was tested in triplicate reactions. All 50 test samples were negative for pCMV genomic equivalents (Table 2). For TGEV, 9 out of 50 samples tested positive but near the assay sensitivity of ^{(b) (4)} per reaction as shown in the table 2.

Table 2 Determination of the initial enveloped viral load: Results from Q-PCR

V. Summary

- a. Sovaly's manufacturing process is capable of providing (b) (4) logs inactivation of enveloped viruses. The manufacturing process has a limited capacity to inactivate non-enveloped viruses. Therefore, a routine testing has been performed for zoonotic non-enveloped viruses, HEV, EMCV, SVDV and Rota A by Q-PCR. The data showed that results were negative for EMCV, SVDV and Rota and 5% of lots tested positive for HEV. All HEV positive lots (by QPCR) were rejected since an infectivity assay is not yet available. Based on the detection limit (DL) for Q-PCR assays, genomic equivalents estimated per gram of pancrelipase for SVDV (b) (4), HEV (b) (4), EMCV (b) (4), and Rota A (b) (4) respectively. The manufacturing process is capable of inactivating non-enveloped model viruses EMCV by (b) (4) log (b) (4) and Reo-3 by (b) (4) log (b) (4). Reo is a model for Rota. The sponsor has established, and validated infectivity assays for, EMCV, SVDV, Rota and PPV. Positive lots by Q-PCR will be evaluated by infectivity assay. However because the overall capacity to inactivate viruses is on the order of (b) (4) logs and the tests are only sensitive to (b) (4) log of viral loads the PCR assays do not appear to be sufficiently sensitive to provide adequate assurance that when these viruses are not detected by QPCR, process capability for inactivation of non-enveloped viruses is not exceeded (*see PMC 2*). Also for clarification, the virological testing specifications for infectivity should be revised to undetectable for zoonotic viruses (*see PMC 5*) and not set based on the limit of detection or quantification.

Regarding PCV1, 2 and Reo viruses, Solvay has not tested these viruses for their DS. We know that the PCV 1 and 2 viruses are present in the PEP product PEP products manufactured by other producers. There is no clear evidence whether PCV 1 or 2 can infect humans. However, antibodies against PCV 1 were detected in hospital patients (Tischer I, et al., Arch Virol. 1995; 140 (8): 1427-39). Since there is a slight possibility that PCV 1 or 2 could infect humans and the presence of live PCV1 and 2 is likely in the drug product. We suggest that Solvay establish a specification for both PCV1 and PCV2 infectivity to further minimize risk to patient safety (*see PMC 3*). Although Reo virus is not associated with any significant human disease it does infect humans. Reo virus infection occurs often in humans in respiratory and intestinal tracts, but most cases are mild or subclinical, usually without disease symptoms. Recently a bat Reovirus was noted as causing a human respiratory disease. While Reovirus is unlikely to be present in pig populations and the route of infection reduces the risk of exposure via an oral route, we believe the risk associated with a zoonotic transmission to humans can be further minimized with a strong proactive program of monitoring pigs for new viruses and routine testing. Based on the lack of a significant disease, Reo virus presents a low risk to patient safety. Thus, consistent with the recommendations from the advisory meeting this virus need not be routinely monitored.

Regarding a novel porcine parvovirus, hokovirus (PHov), Solvay has not provided any information on this virus. PHov shows significant homology to human parvovirus 4 was recently identified in pigs collected from farms or slaughter houses in Hong Kong (Susanna K.P. Lau et al., J. Gen. Virol. 2008, 89, 1840-48). We suggest that Solvay assess the risk to product quality associated with PHov and include a control strategy for mitigating the risk to product quality (*see PMC 4*), if necessary.

Regarding risk mitigation plans for control of novel adventitious agents, Solvay should provide to the Agency their detailed plans for: a) the animal disease surveillance program and continued risk assessment evaluation for source animals; b) assessment of the risk to product quality due to the potential infection of swineherds with parasites; and c) preventing cross-contamination with material from other species, particularly with ruminant tissues (*see PMC 6,7,and 8*).

VI. Post-marketing Commitments for Viral Safety Control

Postmarketing commitments subject to reporting requirements under 21 CFR 314.81

Regarding viral safety control we propose the following post-marketing commitments:

1. 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. The final report and changes to Solvay's control strategy will be submitted to the Agency by [INSERT DATE].
2. Solvay commits to develop sensitive qPCR assays that provide adequate assurance that process capability for the inactivation of non-enveloped viruses is not exceeded. The revised assay and assay validation data, together with new action limits, will be submitted to the Agency by [INSERT DATE].
3. Solvay commits to develop and implement specifications for infectious porcine circoviruses (PCV) 1 and 2 in the final product. The proposed specifications, including relevant method validation, will be submitted to the Agency by [INSERT DATE]. The final specifications will be developed and implemented by [INSERT DATE].
4. 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. The final risk assessment and control strategy will be submitted to the Agency by [INSERT DATE].
5. 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." The revised acceptance criteria will be submitted to the Agency by [INSERT DATE].
6. 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. The final plans will be submitted to the Agency by [INSERT DATE].

7. Solvay commits to assess the risk to product quality due to the potential infection of swineherds with parasites. The final risk assessment and control strategy will be submitted to the Agency by [INSERT DATE].
8. Solvay commits to provide a detailed description of its plans for preventing cross-contamination with material from other species, particularly with ruminant tissues. The final plans will be submitted to the Agency by [INSERT DATE].

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/s/

Ennan Guan
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Barry Cherney
3/31/2009 12:41:12 PM
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Amy S Rosenberg
4/28/2009 01:37:31 PM
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Submission: NDA 20725
Product: CREON[®] (Pancrelipase delayed-release) Capsules 6,000, 12,000, 24,000 Units
Indication: Exocrine pancreatic insufficiency
Formulation: Oral, capsule, enteric coated microspheres

Date: November 17, 2006
Sponsor: Solvay Pharmaceuticals, Inc.

CMC Reviewer: Wei Guo, Ph.D., HFD-122
Through: Gibbes Johnson, Ph.D., HFD-122, Chief, Lab of Chemistry
Barry Cherney, Ph.D., HFD-122, Deputy Director, DTP
Review Date: July 27, 2007

Conclusion: Approvable, send the following comments to the sponsor:

1. Due to the critical role of (b) (4) in lipase activity, adequate control of (b) (4) activity must be ensured in drug substance and product. We recommend that the measurement of lipase potency in release and stability testing be performed in both the absence and presence of (b) (4). Acceptance criteria for activity under each assay condition should be established and justified.
2. The olive oil used as lipase substrate has an acceptance criterion of (b) (4) at (b) (4) of the total fatty acids, but your testing results of nine batches have (b) (4) levels which vary from (b) (4). Please adjust the acceptance criteria of (b) (4) to reflect this fact to ensure that a consistent substrate is used in the lipase potency measurements.
3. Dissolution testing of drug product should be performed on intact capsules.
4. Please define the acceptance criterion of the HPLC identity test used for drug substance and product.
5. Please provide the drug substance and product release test sampling plans.
6. The acceptance criterion of lipase activity for individual capsules tested was changed to (b) (4) of label claim on and after page 0151 of volume 1, submission dated March 21, 2007. It is inconsistent with the proposed acceptance criteria of (b) (4) of label claim on pages 0118, 0127, 0131, 0134, and 0137 of the same submission. Please address this inconsistency.

- 7. Please provide information on the manufacturer and specifications of container, closure, and seals for drug substance packaging.**
- 8. Please provide representative certificates of analysis of seals used in drug substance container/closure system.**
- 9. Drug product labeling has been proposed as [REDACTED] ^{(b) (4)}**
[REDACTED]
Please specify the length of time excursions in temperature that are permitted.

CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

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Introduction:

NDA 20725 was first submitted in 2003. FDA sent a Not-Approvable Letter to the sponsor on October 9, 2003. The sponsor sent this submission as the response to this Not-Approvable Letter and FDA comments dated June 6, 2003, August 20, 2003, and July 23, 2004.

In this submission, the sponsor changed the source of the drug substance from SPL to Solvay. The sponsor also modified drug product formulation.

This review is focused on CMC only. Part A reviews the sponsor's responses to the deficiencies identified in the previous reviews. Part B reviews the new information submitted regarding new drug substance and modified drug product formulation. Part C contains the assessment of the information FDA requested in this review cycle. The viral safety issues are reviewed separately by Dr. Ennan Guan (HFD-122).

Summary of Drug Substance and Drug Product Specifications and Stability Data

1. Drug Substance Release Specifications and Stability Data:

Tests performed in release and stability:

Test and Method	Specification
Characters - Appearance and description	beige-white powder

(b) (4)



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/s/

Wei Guo
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Amy S Rosenberg
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NDA 20-725

Creon Capsules

Solvay Pharmaceuticals Inc.

Martin Haber, Ph.D.

Division of Metabolic and Endocrine Drug Products

Consult Review for:

**Division of Gastro-Intestinal and Coagulation Drug
Products**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 20-725
2. REVIEW #: 2
3. REVIEW DATE: June 29, 2004
4. REVIEWER: Martin Haber, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Memo to file regarding 3/5/04 Communication	4/14/04
Communication from Solvay regarding a proposed new source for drug substance	3/5/04
FDA Not Approvable Action Letter	10/9/03
FDA Discipline Review Letter	8/20/03
Chemistry Review #1	8/18/03
Amendment	8/8/03
Amendment	7/9/03
FDA Information Request Letter (filing review)	6/6/03
Amendment (Complete NDA CMC resubmission)	12/16/02
Original NDA submission	7/31/97

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	10/21/03

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Solvay Pharmaceuticals Inc.
Address: 901 Sawyer Road, Marietta, Georgia 30062
Representative: Donald Ruggirello
Telephone: 770-578-9000

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Creon
b) Non-Proprietary Name (USAN): Pancrelipase (sometimes referred to as Pancreatin)
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3, 7
 - Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Pancreatic Enzyme Insufficiency

11. DOSAGE FORM: Delayed-Release Capsules (enteric coated minimicrospheres)

12. STRENGTH/POTENCY: 5000, 10000, or 20000 Lipase units per capsule

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Pancreatin/Pancrelipase, USP, is a crude mixture of digestive enzymes, principally α -**amylase**, **lipases** (pancreatic lipase, (b) (4) and **proteases** (mainly (b) (4) prepared from hog pancreas tissue (b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS/ REVIEWER
9469	II	SPL	Pancreatin	1	Inadequate	8/9/03	Drug Substance/ Haber
(b) (4)				3	Adequate	5/3/02	Frankewich
				3	Adequate	7/17/02	Shaw
				3	Adequate	5/3/02	Frankewich
				3	Adequate	9/9/99	Vidra
				3	Adequate	2/25/03	Rodriguez
				3	Adequate	6/9/03	Christner
				3	Adequate	8/11/99	Christodoulou
				3	Adequate	6/9/03	Zimmerman
				3	Adequate	8/30/01	Frankewich
				3	Adequate	4/16/04	Frankewich

Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	47546	Creon 10 (pancrelipase) delayed release capsules from Solvay Pharm.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	AC	2/4/04	
Pharm/Tox	AC	9/4/03	Dr. D. Joseph
Biopharm	AE	9/24/03	Dr. S. Al-Fayoumi
Methods Validation	Pending		
OPDRA=DMETS	AC?		
EA	AC, Exclusion requested	NA	NA
Microbiology	NA for this review		

AC = Acceptable, NA = Not Applicable

Executive Summary Section

The Chemistry Review for NDA 20-725

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable at this time

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is a very crude mixture of digestive enzymes, principally α -amylase, lipases (pancreatic lipases, (b) (4) and proteases (b) (4)). It is prepared by **Scientific Protein Laboratories**, Waunakee, WI, (Type II DMF 9649 holder) from (b) (4)

The enzymes of the drug substance are not well characterized or controlled, see discussion below. The drug substance is stored at room temperature and is also very unstable.

The drug product is Creon delayed-release Capsules, in three strengths, labeled to contain 5000, 10000, or 20000 Lipase units/capsule. The three capsule strengths are also labeled to contain 18750, 37500, or 75000 Protease units/capsule and 16600, 33200, or 66400 Amylase units/capsule, respectively. However, product capsules do not contain the labeled amount of enzyme, see discussion below. Creon Capsules are indicated for adult and pediatric patients with exocrine pancreatic insufficiency. Creon Capsules are packaged with coil and a desiccant in 12, 100 and 250 count HDPE plastic bottles with plastic closures.

The drug product capsules contain delayed-release “minimicrospheres” or about (b) (4) diameter particles of the enzyme mixture that are enteric coated with hypromellose phthalate, polyethylene glycol, mineral oil, dibutyl phthalate and dimethicone to protect them from the acid in the stomach. The enteric coating is designed to break down at higher pH (above 6) in the duodenum and release the active enzymes. All three strengths of hard gelatin capsule contain identical minimicrospheres and the active strength of the capsule is determined by the amount

Executive Summary Section

of minimicrospheres that it contains with a larger capsules size containing more minimicrospheres. Drug product capsules are manufactured by Solvay Pharmaceuticals GmbH, in Neustadt, Germany. The chemical manufacturing and controls for the drug product capsules are deficient, see discussion below.

Some clinical trials were conducted with a different formulation containing a different, larger “microsphere” formulation. This microsphere formulation contained the same active and inactive components in different amounts. Other strengths (e.g., 8,000; 12,000 or 25,000 Lipase units/capsule) were also used in some supportive clinical trials.

B. Description of How the Drug Product is Intended to be Used

The usual initial starting dose is 10,000-20,000 lipase units per meal. Doses are taken during meals in order to aid digestion. The draft labeling recommends (b) (4)

The maximum daily dose is unclear. The proposed expiration dating period is (b) (4) but this is not supported by stability data since the product is unstable, see discussion below. The recommended storage condition is controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance is an extremely crude natural product material, derived from hog pancreas. There is no characterization data available. Consistency with respect to chemical identity and biological activity has not been demonstrated. The proposed specifications for drug substance (based on the USP monograph) are inadequate. More appropriate specifications based on characterization data and including tests for identity, biological activity, purity, impurities, and degradants are needed. The proposed use of (b) (4)

The viral safety evaluation has not yet been completed. The drug substance is markedly unstable at room temperature, the proposed storage temperature.

The drug product has historically been formulated with large stability overages or with only a lower limit on the enzyme activity. The proposed drug product specifications are similar to those proposed for the drug substance and are inadequate with extremely broad proposed acceptance limits. Normally, drug product specifications are proposed based on drug substance specifications. Until adequate drug substance specifications are established, drug product specifications cannot be finalized. Until the drug product specifications are established, stability testing and expiration dating cannot be established. The drug product is also unstable.

Executive Summary Section

An initial filing review and IR letter with several chemistry deficiencies was issued by the Agency and the IR letter was sent to Solvay on 6/6/03. The firm made very preliminary responses in the 7/9/03 and 8/8/03 Amendments which were reviewed in Chemistry Review #1, dated 8/18/03. The major chemistry deficiencies were and are:

- Drug Substance Characterization – Inadequate, characterization was never done
- Drug Substance Reference Standards – Inadequate, present standards are crude uncharacterized material
- Drug Substance Specifications – Inadequate, requires specific tests for identity and purity
- Drug Substance Viral Safety Evaluation – Inadequate, not completed
- Drug Substance Stability – Inadequate, stability is poor

- Drug Product Specifications – Inadequate, requires specific tests
- Drug Product Stability - Inadequate, cannot be evaluated until tests are established

A CMC DR letter was sent to Solvay on 8/20/03 that conveyed comments from Chemistry Review #1. An NDA NA letter from the FDA was issued on 10/9/03.

The firm provided a preliminary response to some of the CMC items in the FDA's 8/20/03 DR letter in **the 10/21/03 Amendment**, which is reviewed in this chemistry review (Chemistry Review #2). The firm's complete response to most of the chemistry deficiencies in the NDA is still pending.

Additional comments from this review should be conveyed to the firm, see Draft Letter. The NDA remains not approvable from a chemistry viewpoint.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

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

/s/

Martin Haber
6/29/04 03:43:07 PM
CHEMIST

Liang Zhou
6/29/04 05:28:52 PM
CHEMIST

The reviewer's comments should be conveyed to the Applicant.

NDA 20-725

Creon Capsules

Solvay Pharmaceuticals Inc.

Martin Haber, Ph.D.

Division of Metabolic and Endocrine Drug Products

Consult Review for:

**Division of Gastro-Intestinal and Coagulation Drug
Products**

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Chemistry Review Data Sheet

1. NDA 20-725
2. REVIEW #: 1
3. REVIEW DATE: August 18, 2003
4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA submission	7/31/97

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	8/8/03
Amendment	7/9/03
Amendment	12/16/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Solvay Pharmaceuticals Inc.
Address:	901 Sawyer Road, Marietta, Georgia 30062
Representative:	Donald Ruggirello
Telephone:	770-578-9000

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Creon
b) Non-Proprietary Name (USAN): Pancrelipase (sometimes referred to as Pancreatin)
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3, 7
 - Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Pancreatic Enzyme Insufficiency

11. DOSAGE FORM: Delayed-Release Capsules (enteric coated minimicrospheres)

12. STRENGTH/POTENCY: 5000, 10000, or 20000 Lipase units per capsule

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Pancreatin/Pancrelipase, USP, is a crude mixture of digestive enzymes, principally **α -amylase**, **lipases** (pancreatic lipase, (b) (4) and **proteases** (b) (4) prepared from hog pancreas tissue after (b) (4)

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS/ REVIEWER
9469	II	SPL	Pancreatin	1	Inadequate	8/9/03	Drug Substance/ Haber
(b) (4)				3	Adequate	5/3/02	Frankewich
				3	Adequate	7/17/02	Shaw
				3	Adequate	5/3/02	Frankewich
				3	Adequate	9/9/99	Vidra
				3	Adequate	2/25/03	Rodriguez
				3	Adequate	6/9/03	Christner
				3	Adequate	8/11/99	Christodoulou
				3	Adequate	6/9/03	Zimmerman
				3	Adequate	8/30/01	Frankewich

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	47546	Creon 10 (pancrelipase) delayed release capsules from Solvay Pharm.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	NA		
Biopharm	Pending		
LNC	Pending		
Methods Validation	Pending		
OPDRA=DMETS	Pending		
EA	Acceptable, Exclusion requested	NA	NA
Microbiology	NA		

The Chemistry Review for NDA 20-725

The Executive Summary

I. Recommendations

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Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Pending

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(b) (4) The enzymes of the drug substance are not well characterized or controlled, see discussion below. The drug substance is stored at room temperature and is also very unstable.

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Executive Summary Section

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The maximum daily dose is unclear. The proposed expiration dating period is (b) (4) but this is not supported by stability data since the product is unstable, see discussion below. The recommended storage condition is controlled room temperature.

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(b) (4)
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III. Administrative**A. Reviewer's Signature**

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

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/s/

Martin Haber
8/18/03 12:37:57 PM
CHEMIST

list of deficiencies is attached at end of review

Ali Al-Hakim
8/19/03 12:27:31 PM
CHEMIST
Ali Al-Hakim for Liang Zhou