CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-210

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Center for Drug Evaluation and Research - Food and Drug Administration
Office of Biotechnology Products, Office of Pharmaceutical Science
29 Lincoln Drive, Bethesda, MD 20892

DATE: August 17, 2009

FROM: Howard Anderson, Ph.D. Biologist, DTP/OBP/OPS/CDER

THROUGH: Emanuela Lacana, PhD, Associate Chief Laboratory of Chemistry
Gibbes Johnson, PhD, Chief Laboratory of Chemistry
Barry Cherney, PhD, Deputy Directory Division of Therapeutic Proteins

SUBJECT: Product Quality Review of Complete Response, Dec.22, 2008 Submission Pancreatic Enzyme Product (PEP) Delayed-Release Capsules 5,000, 10,000, 15,000, & 20,000 U USP/capsule

NDA: 22-210

DRUG PRODUCT: ZenPep (Pancrelipase Delayed Release Capsules)

MANUFACTURER: Eurand Pharmaceutical Limited
The Yard House
Kilruddery Estate
Republic of Ireland

API/DRUG SUBSTANCE: DMF 7090 (Reviewed by Dr. Anderson and Dr. Guan in a separate document)

OND/ODE III: Division of Gastroenterology Products
RPM: Elizabeth Ford

RECOMMENDATION: **I recommend approval of NDA 22-210.** One deficiency was identified in the NDA and it can be addressed as a PMC. Deficiencies exist with DMF 7090, but do not preclude approval of this application since they can be addressed as PMC's. The NDA and DMF 7090 PMCs are provided on the next page.

POST-MARKETING COMMITMENTS

NDA 22-210 POST MARKETING COMMITMENT

1) Eurand commits to reevaluate the acceptance criteria for the protease and amylase assays after more experience is gained with the manufacturing process. After **[insert number]** of drug product lots are manufactured specifications will be reevaluated and adjusted to reflect manufacturing history and capability. The information will be provided to the FDA by **[insert date]**.

DMF 7090 POST MARKETING COMMITMENTS

1. Develop and validate an infectious assay for PCV1.

   Final Report Submission: by MM/YY

2. Establish lot release specifications for PCV1 for the drug substance.

   Final Report Submission: by MM/YY

3. Establish lot release specifications for PPV and PCV2 for the drug substance.

   Final Report Submission: by MM/YY

4. Perform additional monitoring of enveloped viral load entering the manufacturing process. The control program will include the selection of human pathogenic enveloped viruses for monitoring by qPCR together with an appropriate control strategy.

   Final Report Submission: by MM/YY

5. Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. Revise the assays, and submit assay validation data, together with acceptance criteria.

   Final Report Submission: by MM/YY

6. Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.

   Final Report Submission: by MM/YY

7. Improve the animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program will include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.

   Final Report Submission: by MM/YY

8) Assign an expiration date to the pancrelipase drug substance label used for production of the Zenpep product. An expiration date will be included on the drug substance label by **[insert date]**.

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The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of NDA #22-210 for ZenPep pancrelipase manufactured by Eurand Pharmaceuticals. The data submitted in this application support the conclusion that the manufacture of pancrelipase is controlled, and leads to a product that is consistent and potent. The conditions used in manufacturing have been validated, and a consistent product is produced by the process. It is recommended that this product be approved for human use (under conditions specified in the package insert).

Although some lots of pancrelipase have been shown to contain infectious porcine parvovirus (PPV), the risk that PPV can cross species and transmit diseases to humans is minimal, and is outweighed by the clinical benefit provided by pancrelipase.

B. Recommendation on Post-Marketing Commitments (PMC)

On page 2 of this review are the PMCs that should be addressed. They concern the drug substance label, improving viral detection assays and surveillance strategies during manufacturing of the drug substance, and tightening acceptance criteria for the drug product amylase and protease potency assays.

II. Summary of Chemistry Assessments

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

- General: Pancrelipase is the USAN name for the active pharmaceutical ingredient in ZenPep®, and is a complex mixture of proteins obtained from porcine pancreas. Pancrelipase contains amylase, lipase, (b) (4)

- Complexity: As described above, the product is a complex mixture of different proteins present in the pancreatic extracts. The pancreatic extracts have been characterized based upon their enzymatic activities, and by using analytical techniques such as Isoelectric focusing, SDS-PAGE, Reverse-Phase HPLC and by two dimensional SDS-PAGE. Protein sequencing and Mass Spectrometry were employed to identify RP-HPLC peaks and 2D-SDS-PAGE spots, respectively.

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

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22210	ORIG 1		ZENTASE
NDA 22210	ORIG 1		ZENTASE

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

/s/

HOWARD A ANDERSON
08/18/2009

EMANUELA LACANA
08/18/2009

BARRY W CHERNEY
08/18/2009

From: Ennan Guan, MD/Ph.D
To: NDA: 22210
Through: Barry Cherney, Ph.D. Deputy Director, CDER/OPS/OBP/DTP, HFM541
Product: Zentase
Sponsor: Eurand Pharmceuticals (Drug substance manufactured by Nordmark)
Final Date: June 18, 2008

I. History of pancreatic enzymes products **(PEPs)**

The PEPs are a mixture of digestive enzymes extracted from native porcine pancreas glands. The PEPs have been marketed in an unregulated fashion, since prior to 1938, and principally are used in Cystic Fibrosis (CF) patients, the vast majority of whom take PEPs for their entire lives, as well as in patients with pancreatic insufficiency associated with alcoholism. The impetus to bring PEPs into a regulatory paradigm arose in response to cases of fibrosing colonopathy in the 1990s, which were felt potentially attributable to the PEPs, as in contrast to naturally released pancreatic enzymes, PEPs release further down in the small intestine and even into the colon where high local concentrations may damage colonic epithelium. FDA published a Federal Register notice in 2004 requiring New Drug Applications (NDAs) for these products, and published Guidance for Industry on Exocrine Pancreatic Insufficiency Drug Products in April, 2006. The original deadline for NDA approval of all PEPs was April 28, 2008, which was changed to April 28, 2010 when it

became clear that most manufacturers would not be able to meet the deadline.

In its guidance, FDA stipulated that All PEPs are considered non-interchangeable, that the 505(b)(2) route is the appropriate route for approval, and that to be approved, the NDA must meet requirements in 21 CFR 314.50 for human Pharmacokinetics (PK) and Biological Activity (BA) information and that efficacy must also be demonstrated and should include pediatric patients with CF.

As regards the issue of viral contamination of PEP products, the "Guidance For Industry: Exocrine Pancreatic Insufficiency Drug Products" stated the following:

- "A full viral risk assessment should be performed and justified by the Sponsor"
- "The manufacturing process should be validated for its capability to remove and/or inactivate viral agents as recommended in ICH Q5A" (Viral Safety Evaluation of Biotechnology Products derived from Cell lines of Human or Animal origin).

It should be noted that ICH Q5A sets a very high standard in demanding the best reasonable assurance that the product is ***free of virus contamination*** and requiring knowledge of how much virus may be present in the starting material.

In fact, the viral safety issues have become more publicized in view of an article in the New York Times on April 1, 2008 (Seeking Alternatives to Animal Derived Drugs) specifically addressing pancreatic enzyme products and stating that the Cystic Fibrosis Foundation is working with the Altus Pharmaceutical Company to develop recombinant pancreatic enzymes. The article also alleges that in 2006, FDA stated that the viruses "must nonetheless be eliminated or rendered inactive", which is not the case. Moreover, two Citizen's Petitions have recently been received at the agency (April 15, 2008) from Altus Pharmaceuticals which largely focus on viral safety issues.

Currently there are three PEP drug substance manufacturers that supply the active ingredient for all PEP drug products.

II. **Risk Identification and Assessment**

A. Origin of Raw Material

The active pharmaceutical ingredients in Pancrelipase manufactured by Nordmark Pharmaceuticals GmbH & Co. KG, Germany, are derived from native pig pancreas tissue. One pancreatin product batch uses up to (b) (4) kg frozen glands from approximately 50,000 pigs. The glands are collected in approved slaughterhouses under continuous inspection of "official" veterinarians ante and post mortem. However, no further information is provided regarding the credentialing program or organization of the inspection "official". The information has been requested from Nordmark in Howard Anderson's review. No SOP for procuring the organs is available. Pigs found to be healthy by visual inspection are declared as fit for human consumption and introduced for slaughter. The gland quality is monitored at receiving and includes visual appearance, veterinarian certification, and demonstration of cold chain maintenance during transportation and storage. The glands are quarantined for 4 weeks to avoid introduction into manufacturing of glands that are associated with a disease outbreak in the source pigs.

Although there is a vendor qualification program, little information was provided regarding this program or even a representative heath certification from the 12 raw material vendors identified in the submission. Howard Anderson noted this deficiency and included a letter comment in his review. We also discussed the feasibility of sourcing animals from closed herds, or herds that had been vaccinated for PCV2 and PPV,and establishing SOPs for organ harvest, storage, and transport. Nordmark maintained the infeasibility of such approaches, given the number of glands needed to produce each lot (50,000) and the inability of slaughterhouses to follow such procedures. From our perspective, this is a very disappointing response, as we strive to ensure the highest quality of raw materials, which would demand control of procurement and shipping procedures. However, this response reflects the requirement for the very large numbers of organs needed to produce each lot and the impracticalities of obtaining this number from defined herds.

(b) (4)

Slaughterhouses from the following countries have been approved and accepted by Nordmark as suppliers for the pancreas glands. It should benoted that no pigs are sourced from China.

Denmark
France
Germany
Netherlands
Spain
USA

Comment: Although we know the location of the slaughterhouses we must verify that the pigs originate solely from the countries listed above and are not imported from Asia etc.. Howard Anderson requested clarification of this issue from Nordmark in his review.

B. Viruses Known to be Present in Swine

The pancreata are derived from pigs raised and slaughtered for food production purposes. Pig populations are known to transmit human pathogens such as influenza A and hepatitis E virus, and are also known to harbor swine viruses that to date have not been found to infect humans, but which do have the potential to cross species barriers, such as porcine parvovirus. The vast majority of pigs for slaughter have not been vaccinated to viruses of concern. Pigs predominantly of US origin are vaccinated to porcine circovirus, and most breeding sows have been vaccinated for PPV, due to fetal wastage from this virus. Thus, the possibility of contamination of the starting material with viruses relevant to both humans and swine is of great concern.

The ability of infectious disease agents to cross species barriers has been long recognized and new viral zoonotic diseases have appeared from time to time which may pose a great danger to humans. Indeed, influenza viruses have both porcine and avian intermediary hosts in generation of human influenza pandemics. It is thus possible that swine can be intermediate hosts for other infectious agents as well. Evidence that porcine parvoviruses, which are highly resistant to routine methods of inactivation, can infect humans is limited thus far to stable cultured human cell lines by a non-pathogenic PPV strain KBSH (Hallauer et al 1971. Archiv fur die gasamte Vursforschun 35:80-90), while no evidence for their infectivity has been observed in pig farm workers (Wattanavijarn W et al. 1985 Trans R Soc Trop Med Hyg 79:561), or in hemophilia A patients treated with porcine factor VIII preparations. (Soucie JM et al 2000. Transfusion 40: 708-711). However, patients consuming PEP products have never been evaluated for infection by porcine paroviruses. Therefore, updated risk identification, risk assessment and animal disease surveillance/prevention are important measures to ensuring the safety of the PEP products.

The porcine viruses can be divided into two broad categories, enveloped and non-enveloped. Based on consulting with CBER, CMV, and USDA scientists, literature searches, and information provided from sponsors, listed below are viruses known to be present in swine.

Enveloped viruses in swine

Enveloped viruses include African swine fever virus, transmissible gastroenteritis virus, classical swine fever virus, bovine viral diarrhea virus, pseudorabiesvirus, swine influenza virus A, porcine endogenous

retroviruses, suipoxivirus, rabies virus, porcine CMV, porcine lymphotropic herpersvirus, West Nile Virus, Hantavirus and Vesicular Stomatitis Virus. Some of these enveloped viruses are transmissible from pigs to humans and can cause disease and have caused pandemics (influenza), includingthe following:

- Influenza virus A (ssRNA, 110 nm, airborne),
- Vesicular Stomatitis Virus (ssRNA, 70-170 nm, aerosols),
- Pseudorabiesvirus (dsDNA, traumatic inoculation) and
- Rabies virus (ssRNA, bite)
- West Nile virus(mosquito bite)
- Hantavirus (Rodent-borne)

Swine are extremely rarely infected with rabies (1-2 cases/year in USA,) (Ref: Dr. Bruno Chomel's presentation "Swine Zoonose", California Department of Food and Argriculture Animal Health and Food Safety Services). Although the pig is the only natural host for pseudorabies (PRV), the State-Federal-Industry PRV eradication program culminated with the declaration by the PRV Control Board at the 2004 United States Animal Health Association (USAHA) meeting that all States had achieved Stage V- PRV-Free status (Eric Bush, National Surveillance Unit, 2006 NASHSS Outlook Quarter One). PRV is mainly in wild pigs in USA.

West Nile Virus (WNV) or Hantavirus due to low exposure (they are typically housed in buildings), low susceptibility to infection or ease of detection and elimination of the infected individuals from the herd. The general consensus is that the primary reservoir of West Nile are birds, especially crows, jays, sparrows, and grackles. The role of mammals, including swine, in the epidemiology of West Nile virus has not been fully evaluated. The results from experimental infection of pigs with WNV showed that pigs did not develop a detectable viremia or seroconvert, suggesting that pigs are not susceptible to WNV and that pigs are unlikely to play a significant role as amplifying hosts of WNV (Diseases of Swine 9^{th} Edition, by Barbara E. Straw, et at. 2006; Teehee ML, et al. Archives of Virology, 150 (6): 1249-56, 2005) Moreover, there is compelling evidence that enveloped viruses are very sensitive to physiochemical treatments (solvent, detergent, and low pH) due to the high lipid content of the envelope, and that they can also be effectively inactivated by heating to 55- 60 ^{0}C for 30 min.

Non Enveloped Viruses in Swine

Non-enveloped viruses in swine include Porcine Parvovirus, Encephalomyocarditis Virus, Foot and Mouth Disease Virus, Swine Vesicular Disease Virus, Porcine Teschoviruses, Vesicular Exanthema Virus, Porcine Enteric Calicivirus, Porcine Rotavirus, Porcine Astrovirus-1, Porcine Adenovirus A and B, Porcine Circoviruses1 and 2, Porcine Respiratory and Reproductive Syndrome Virus, Porcine Respiratory Coronavirus, Swine Hepatitis E Virus. Some of these viruses are transmissible from pigs to humans and can cause disease, including the following:

- swine Hepatitis E virus **HEV**(33 nm, RNA, fecal-oral),
- Encephalomyocarditis virus **EMCV**(28 nm RNA, oral),
- swine Vesicular Disease Virus **SVDV**/PEV9 (oral),
- **Reo/Rota** virus (fecal-oral),
- Foot and mouth diseases virus **FMDV**(28nm, RNA, airborne)

Regarding the infectivity of FMDV to humans, in September 2001, FMDV was labeled as "no known transmission to humans" by the French Agency for the Safety of Health Products (AFSSAPS) (September 14, 2001). Although, FMDV has been substantially eliminated from Europe following WWII, an outbreak in the United Kingdom that rapidly spread among farm animals and spread to several EU countries including France (by March 2001) indicates that Foot and mouth disease remains a constant threat to European farm animals. Europe has taken steps to prevent the entry of the FMD virus into their region so risk has been substantially reduced. Nordmark's plans for animal disease surveillance should include the risks associated with out breaks of FMDV (**see comments**)

Non-enveloped viruses displayed various degree of resistance to physiochemical treatment. Some enveloped viruses are somewhat sensitive to physiochemical treatment (Reo, EMCV, etc) and some are highly resistant (e.g. PPV).

Emerging Viruses

There are examples of viruses (HEV, Porcine Respiratory and Reproductive Syndrome Virus, PCV2, Porcine Lymphotropic Herpesvirus and Porcine Respiratory Coronavirus) which appear to have emerged in

pigs over recent years. Several other viruses are present in a wide range of animals as well as in humans, but so far have not been reported in pigs. However, it is theoretically possible that pigs may also be susceptible to infection by agents not documented to have caused porcine infection including the following:

Spumaviruses (Retroviridea; ss-RNA, enveloped)
Lymphocytic chorimeningitis virus (Arenaviridea, ss-RNA, enveloped)
Borna disease virus (Bornaviridae, ss-RNA, enveloped)
Polyomaviridae (papoviridae, ds-NDA, non-envelope)

As these organisms may mutate to adapt and cause infection in pigs, both regulatory agencies and industry should continuously be alert for emerging viruses, and animal disease surveillance should be extended to evaluate for outbreaks of illness caused by novel forms of existing viruses and other adventitious agents adapted to porcines.

Public health concerns of HEV

HEV raises several concerns which are here discussed in detail. HEV, the causative agent of hepatitis E, is a single positive-stranded RNA virus without an envelope that causes enterically transmitted non-A and non-B hepatitis. This disease should not be confused with hepatitis C, also called parenterally transmitted non-A and non-B hepatitis, which is a common cause of hepatitis in the U.S. HEV is classified in a group called hepatitis E-like viruses. HEV is transmitted primarily by the fecal-oral route, and contaminated drinking water is the most commonly documented route of transmission. It is not known to be transmitted through needles, blood or other body fluids or through sexual contact. Hepatitis E is an important public health disease in many developing countries. In these countries, two antigenic types of HEV, Asian type and Mexican type have been identified. A third type of human HEV has been isolated from HEV non-endemic countries, which shows only a limited similarity to Asian or Mexican types, but is similar to swine HEV. The existence of a population of individuals in industrialized countries who are positive for anti-HEV has led to the hypothesis that an animal reservoir(s) for human HEV may exist. In the US, two cases of acute hepatitis E (HEV US-1 and HEV US-2) have been reported, which were genetically distinct from other known strains of HEV, but were closely related to each other and to the USA strains of swine HEV (about 98% amino acid sequence identity). Moreover, several novel isolates of HEV have been identified from

patients in Taiwan which were closely related to strains of swine HEV from pigs in Taiwan. The above evidence indicates that swine HEV is likely a zoonotic agent and has potential for transmission to humans. The potential for cross-species infection by HEV raises a public health concern, particularly for high risk groups such as swine handlers, pig farmers, and meat handlers. Feagins et al (J Gen Virol 88, 912-917, 2007) demonstrated that commercial pig livers sold in local grocery stores in the USA were contaminated by HEV and that the contaminating virus remains infectious. Among the 127 livers from local stores in Blacksburg, VA and Ames, IA that were tested, 14 were positive for HEV RNA (11% positive). Two of the three PCR-positive pig-liver homogenates transmitted infection, as evidenced by detection of fecal virus shedding from inoculated pigs. Yazaki et al reported (J Gen Virol 84, 2351-2357, 2003) that commercial livers sold in local stores in Japan were contaminated with HEV with 7 out of the 363 packages having detectable HEV RNA (1.9% positive) with viral loads ranging from 2 to 7 logs /per gram of liver. The infectivity of these was not tested. Moreover, in Yazaki's report, among ten patients who contracted sporadic acute hepatitis E, nine of them had a history of consuming grilled or undercooked pig liver 2-8 weeks before the disease onset, thus raising a public-health concern for food-borne HEV infection. To date, there have not been reported outbreaks of HEV in the US, only a few sporadic cases.

From Johnson & Johnson's Periodic Safety Update Report (PSUR) during the year 2005 for pancrelipase, there is no suggestion of zoonotic infectious resulting in hepatitis due to swine HEV associated with the use of pancrelipase. Based on the world-wide total sales of (b) (4) capsules, the estimated exposure to pancrelipase in this review period is approximately 12,223,523 patient-days or 407,451 patient-months.

This virus should be considered as a zoonotic agent and should be adequately controlled by rigorous testing and elimination of lots positive for its presence.

Transmission of Encephalomycarditis in Human

EMCV, a non-enveloped virus belongs to the genus cardiovirus in the family picornaviridae. EMCV is a rodent virus that has an extremely wide host range. Transmission has been demonstrated experimentally among pigs kept in close contact, usual farm conditions in most countries. Fatal mycarditis due to EMCV infection has been observed in primates,

elephants, carnivores and rodents with EMCV (Gaskin, J.M, et al. Enncephalomycarditis in Zoo Animals. Proceedings of the Ist International Conferences on zoological and avian Medicine 1978; Wells, et al. J. Zoo and Wild. Med 20(3): 291-296, 1989; Elephant Care International Fact Sheet by Susan Mikota, DVM).Study of the prevalence of EMCV antibodies among selected human populations in various regions of the world revealed antibody rates among children ranging from 1 to 33%, while adults varied from 3.2 to 50%. The pattern of age-specific rates observed in the study populations suggests that EMCV infection occurs primarily during childhood. Sera from diabetic, suspected encephalitis and mycarditis patients were also examined for EMCV neutralizing antibodies. The prevalence of antibodies among these groups was not significantly different from that of control populations in the same geographic regions. The results of this study indicate that EMCV infection in man is fairly common but that most cases are probably asymptomatic and/or unrecognized. There are clinical and pathological reports of fatal encephalitis in young children with associated myocarditis wherein the authors suggested EMCV as the possible etiologic agent, but virus studies were not performed to identify the causal agent. From Johnson & Johnson's PSUR during the year 2005 for pancrelipase, there is no suggestion of zoonotic infections resulting in myocarditis due to porcine EMCV associated with the use of pancrelipase.

EMCV should be considered as a zoonotic agent and should be adequately controlled by testing and elimination of contaminated lots.

Porcine Rotaviruses infection in human

Rota and Reo viruses belong to the Reoviridae family which are non-enveloped small round viruses (~ 75 nm dsRNA). Rotaviruses are resistance to organic solvent treatment but sensitive to heat treatment. Rotaviruses are the most significant cause of severe gastroenteritis in young children and in animals. There are 7 distinct groups (A-G). Group A rotavirus cause diarrhea in pigs. Transmission is via the fecal-oral route. There has been speculation on the role of animal rotaviruses in human infections. By analysis of genome segments, several human strains revealed a NSP4B genogroup and an NSP5/6 gene of porcine origin. This finding suggest interspecies transmission of rotavirus stains and or gene exchange, and may indicate the occurrence of at least 3 separate rotavirus transmission events between pigs and humans, providing convincing evidence that evolution of human rotaviruses is highly intermingled with

the evolution of animal rotaviruses. The main human pathogen is rotavirus which causes diarrhea, mainly in infants while Reo viruses were not known to be an important cause of any human disease.

Rotaviruses should be considered as a zoonotic agent and controlled by testing and elimination of contaminated lots.

Swine Vesicular Disease Virus

SVDV belongs to the genus enterovirus within the Picornaviridae family comprised of a small non-enveloped (30 nm) single-strand RNA genome. The SVDV is resistant to low pH treatment but can be inactivated at 69 ^{0}C. The SVDV is antigenically closely related to the human enterorvirus Coxsackievirus B5 and genetic studies of a number of SVDV stains and epidemiologic information strongly suggest that a human Coxsackie B5 was specifically introduced into and infected swine several decades ago. During infection, viruses can be isolated from both the lower and upper alimentary tracts, and can be transmitted by fecal-oral and respiratory routes. Tissues from pigs killed during the viremic period contain up to 10 million infectious particles per gram. Moreover, infection can occur via skin or mucosal lesions with succeeding formation of a primary vesicle. Cross-species infection, from pigs to humans with SVDV does not result in clinical signs. In lab personnel handling SVDV, seroconversion was observed in some cases without any signs of disease.

Although infection does not appear to result in clinical symptoms, SVDV should be still considered as a zoonotic potential agent and should be adequately controlled by testing and elimination of contaminated lots. Since SVDV evolved from Coxsackie B virus serotype 5 in the recent past, crossing the species barrier from humans to pigs, and still can infect humans, the patients who take PEPs may be vulnerable to SDVD infection and potentially become ill Indeed, three DS producers' viral experts all suggest that SDVD is a potential zoonotic pathogen.

Porcine Circovirus

PCV is a small non-enveloped negative-sense, single strand DNA virus (17 nm). Circoviruses are frequently found in birds and plants, but pigs are the only mammalian species from which the virus has been isolated. There are two types of virus that have been identified, types 1 and 2.

Despite its high serologic prevalence, PCV1 virus is non-pathogenic in pigs. In contrast, PCV2 is associated with post-weaning multi-systemic wasting syndrome in pigs, an agriculturally significant problem. The prevalence of seropositivity to PCV2 among individuals with close and prolonged contact with pigs was studied in 50 volunteer veterinarians working closely with pigs. The study showed no antibodies to PCV1 or PCV2. There is no additional evidence that humans have been infected with circovirus during normal contact with swine and swine products. Since early 2007, pigs (principally in the USA) have been vaccinated with porcine circovirus. Thus, pigs sourced from the US are expected to have a significantly decreased PCV load .

PCV is not considered as a zoonotic agent. Levels should be monitored for product quality control purposes and not for potential to transmit disease.

Foot and Mouth Disease Virus

FMDV is a species in the Aphthorirus genus of the picornaviridae family and contains a single stranded RNA genome and a non-enveloped capsid. The virus is reported to be acid-labile and may not spread to most humans via consumption of infected meat because stomach acid will completely inactive FMDV. However, the virus may not be destroyed in those patients in whom stomach acid is neutralized by iatrogenic means for peptic ulcer disease or gastric reflux syndromes. Nonetheless, humans have a low susceptibility to this virus, suggesting other modes of resistance. Seven serotypes have been identified. FMDV is one of the most highly contagious livestock disease in the world with potentially severe economic consequences. Foot lesions are the most common. Morbidity of FMD approaches 100% but the fatality rate does not exceed 5%, except that higher fatality rates are observed in young piglets. There is no treatment for FMD. Vaccination may be used to control outbreaks. It may be transmitted to humans by contact or ingestion but infection in human is extremely rare and requires direct exposure to massive amounts of virus (Q&A: The risks to humans BBC News, April 25, 2005). Infection with FMDV in humans causes a transient low-grade fever with vesicles on the lips, hands and occasionally on the feet, as well as an, in the mouth. Recovery is rapid and uneventful. The FMDV has recently been designated as causing “no known transmission to humans” by the French Agency for the Safety of Health Products (AFSSAPS) at the 14 September 2001 meeting. The seeming contradiction relates to the control

and elimination of the disease following World War II. In 1996, endemic areas included Asia, Africa, and parts of South America. As of August, 2007, Chile is disease free, and Uruguay and Argentina have not had an outbreak since 2001. North America, Australia and Japan have been free of FMD for many years and New Zealand has never had a documented case of foot and mouth disease. Most European countries have been recognized as disease free, and countries belonging to the European Union have stopped FMD vaccination in 1991.

In general, the FMDV is not considered a human health hazard because humans are considered not to be particularly susceptible to infection and importantly, Europe, North America, Australia and Japan are disease free. It should be stipulated that porcine glands used for production of PEPs must originate from FMD free countries or testing and specifications will need to be set.

PPV

PPV is a member of the parvoviridae family. PPV is a very small (18-26 nm) non-enveloped capsid. It is extremely resistant to common physiochemical treatments and can withstand 100 ^{0}C for 30 min. Undercooked pork products are likely contaminated with live PPV. Although most herds have been infected with PPV the virus is only pathogenic to reproduction sows and causes reproductive failure. Therefore, vaccination is restricted to reproduction sows.

Thirty four Pancrelipase DS batches were tested by Q-PCR . The PPV genome was detected in all samples with comparable concentrations, irrespective of the sources of the pigs and the independent production processes from three different pancrelipase producers. The number of genome copies ranged from 2×10^6 to 1×10^7 copies/gram and the average was 5×10^6 copies/gram pancrelipase. The titer of infectious PPV viruses was analyzed in two different batches per company (6 in total) out of the 34 samples described above. Although the validity of this investigation had been challenged by the potential contribution of the cytotoxicity of indicator cells by pancrelipase, this was addressed by testing in the presence of protease and lipase inhibitors. The results revealed that in 6 samples, 2 to 3 $\log_{10}$ of infectious PPV particles per gram pancrelipase were detected. No reduction of PPV infectivity was observed during the different steps of the pancrelipase production process as revealed by infectivity assays. Extensive literature searches revealed

that PPV has not been transmitted to humans under natural conditions (contact, food, etc) to date. A study report showed neither clinical disease nor seroconversion in 56 pig farm staff following close contact with PPV-infected pigs for at least a year (Wattanavijarn W et al. 1985 Trans R Soc Trop Med Hyg 79:561). Moreover, patients who received HYATE C (porcine factor VIII) did not develop anti-PPV antibodies (Soucie JM et al 2000. Transfusion 40: 708-711). In addition, PPV has not been found to infect primary human cells, although one group reported infection of a stable human cell line with the nonpathogenic PPV strain, KBSH (C. Hallauer, et al. 1972, Archiv fur die gesamte virusforschung). However, patients consuming PEP products, who have a high level of exposure via the natural route, have never been evaluated for infection by porcine paroviruses.

Investigation into the possibility of cross species transmission has revealed that the ability of parvovirus to cross species barriers depends on both their ability to bind to and internalize into foreign cells, as well as to efficiently utilize cellular machinery to generate viral DNA, RNA and proteins. Thus, the basis for cross species infection of canids by Feline Parvovirus was mutations in critical areas of the viral capsid that allowed binding and internalization into canid cells. Adaptation involved a series of small but specific changes in the capsid surface (VP2 aa 93, 300 and 323) that changed the viral-host tropism to allow infection in the dog (Karsten Hueffer, et al., Current Opinion in Microbiology, 2003). Moreover, canid cells apparently provided the critical intracellular elements for parvoviral DNA, RNA and protein synthesis.

For PPV, infection of human cells has only been observed in vitro, in a human cancer cell line, and with a strain of PPV that was not pathogenic (KBSH, C. Hallauer, et al. 1972, Archiv fur die gesamte virusforschung). The lack of evidence to date that PPV has caused bone fide infection in humans, despite prolonged intimate external and internal contact with swine or swine derived materials, respectively, over millenia and the failure of pathogenic PPV to produce productive infection in a human cell line (Oraveerakul K et al. 1992. J. Virol.) suggests that multiple elements, both extra and intracellular restrict PPV replication in human cells, and thus their ability to cause productive infection. Therefore, in my opinion (Ennan Guan, the primary reviewer) a risk of PPV cross-species infection of human is extremely low.

Contributing to the risk assessment of human infection for PPV is the management of risk of human parvovirus infections from blood transfusions. In that light, human parvovirus B19 is prevalent in human populations. It commonly causes fifth disease (erythma infectiosum) a self limited disease of children but less commonly, B19 may cause transient aplastic crisis (TAC) in persons with sickle-cell anemia and serious complications during pregnancy (e.g. abortion, fetal anemia, hydrops fetalis).
Of importance in risk management, establishments for whole blood donations have not yet implemented parvovirus B19 NAT screening in a minipool format to identify individual reactive donors prior to release of their blood components for transfusion, despite the potential risk to patients with sickle cell disease. Hence it is very likely that B19 positive blood units, along with their components (platelets, red blood cells, and etc) are currently being used to transfuse recipients including those with sickle cell anemia. Thus, in the case of a known human pathogen, parvovirus B19, because mitigation of risk would seriously impact the blood supply, risk is not mitigated. Similarly, mitigation of the theoretical risk of PPV to human, by either curtailing source pigs to those from vaccinated herds, or closed herds, or by treating the pancrelipase product under conditions that would eliminate PPV, is not feasible as there would not be a sufficient supply to meet product demand and, in the latter case, such conditions would inactivate the enzymes, rendering them ineffective.

Although PPV has not been shown to be infectious to humans the ability of parvoviruses to alter their host range and pathogenic properties with relatively minor genetic change (e.g. emerging of CPV-2b to infect both cat and dog) is of concern. Additional studies that elucidate the ability of PPV to infect humans, even if only transiently, should be performed including an evaluation of PEP consuming CF patients for the presence of PPV antibodies. Also there is potential value in monitoring viral loads as a surrogate marker for the general health of the herds and for product quality.

III. Risk Mitigation

To mitigate the risk from adventitious agents the applicant performed an evaluation of the capacity of the manufacturing process to remove viruses and viral testing of enveloped viruses.

A. Viral Clearance Studies

Pancrelipase manufacturing process is as previously described in Section IIA

Selection of Model Viruses

Generally, model viruses selected for viral clearance and validation should include a) relevant viruses that are known to or likely contaminate the source material; b) a broad range of virus types that displays different physicochemical properties; and c) selected model viruses that can be grown as a high titer stock and can be detected with a sensitive and reliable infectivity assay. Listed in the table below are viruses that selected as representative relevant model viruses for evaluation of the pancrelipase manufacturing process for viral clearance.

Model Viruses

Virus Species	Virus Family	Enveloped Genome	Size (nm)	Resistance to Physico-Chemical treatment	Investigated step
PPV	Parvoviradea	No/DNA	20	Very high	(b) (4)
PEV9 (SVDV)		No/RNA		medium	
EMCV	Picornavirida	No/RNA	25-30	medium	
Reo	Picornavirida	No/RNA	40-50	medium	
Rota A		No/RNA		medium	
FCV	Caliciviridae	No/RNA	40-50	medium-high	
PRV	Herpersvirida	Yes/DNA		low	
BVDV	Flaviviridae	Yes/RNA		low	

Rationale for the selection of above viruses:

BVDV (bovine viral diarrhea virus) is chosen as a model to cover the enveloped RNA viruses such as the influenza virus which has zoonotic potential. With regard to animal epidemics, it also serves as a model for another pest-virus, the classical swine fever virus. BVDV shows low resistance to physical and chemical agents.

PRV (pseudorabies virus) belongs to the group of large, enveloped dsDNA viruses that show rather low resistance against physical and chemical treatment. PRV is a model for the herpesviridae family in general and the pig relevant PRV in particular.

PEV9 (SVDV) is a small, single-stranded non enveloped? RNA virus. It belongs to the human enterovirus B family and is thought to have evolved from the human pathogen Coxsackievirus B5, with which it shares a close antigenic and genetic relationship. It represents a model for swine Vesicular Disease Virus, and other pig relevant enteroviruses such as Teschen/Taalfan viruses and is resistant to physical and chemical agents.

EMCV (encephalomyocarditis virus) and Reo III (reo virus type III) are single-stranded small non-enveloped RNA viruses with medium resistance properties against physical and chemical treatments. They represent models for picornaviridae including Foot and Mouth Disease Virus, Swine Vesicular Disease Virus, and other pig relevant enteroviruses such as Teschen/Taalfan viruses and the pig relevant EMCV in particular.

FCV (feline calicivirus) is a non-enveloped ss-RNA virus, primarily selected to model HEV, which is known to exist in pigs as well as to infect humans. The rationale is based on data that places HEV in the Caliciviridae family. However, there is controversey regarding the validity of this classification and thus, no model virus is commonly agreed to represent HEV. There is no established in vitro culture system for HEV.

PPV (porcine parvovirus) is a member of non-enveloped ss-DNA viruses. PPV shows extremely high resistance to physical and chemical treatments. It is directly relevant to the product as well as being included to challenge the inactivation capacity of the production process.

The model viruses selected cover the physical and chemical properties of all relevant potential viral pathogens associated with pancrelipse and most of the relevant viruses. The general plan is suitable for validation of the manufacturing process for viral clearance in accordance ICH Q5A guidelines.

A. Viral Inactivation/Clearance studies

(b) (4)

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

how close are we to not effectively clearing viruses is unknown) (**see comments to the MF**).

Overall, Nordmark's manufacturing process may provide for an acceptable capacity for viral inactivation of enveloped viruses (pending responses to our questions) and inadequate viral inactivation for non-enveloped viruses. However, without additional data, this is not at all assured.

Questions

1. Please provide data supporting the validation of the Q- PCR tests used to estimate viral loads of both enveloped and non-enveloped viruses. Please include information on the selection of the primers, assay specificity, sensitivity (LOQ/LOD), linearity and precision, system suitability criteria (including recovery), along with the SOPs for the test protocols. Please explain the poor sensitivity of these assays and endeavor to improve their power to detect viruses.

2. Based on the ability of the process to inactivate enveloped viruses, you have proposed not setting specifications for acceptable levels. However, we note that it is difficult to predict the absence of adventitious agents and is particularly challenging when the limit of detection is near the process's capacity to inactivate viruses. We therefore highly recommend that you establish better control of these viruses by setting action limits and specifications for the presence of viral genomes and infectious viruses, respectively.

Non-Enveloped Viral Loads

Results of viral testing by Q-PCR

50 drug substance batches have been investigated for the presence of zoontic viruses HEV, EMCV, PEV9 (SDVD), Rota-A and Reo genomes. Non zoonotic viruses that are thought to be endemic in pig populations i.e., PPV and PCV1, 2 genome load were also monitored. The batches were selected over a time period of one year (January 2006 until December 2006) and from animals of different origins (US and EU) and genders (sows and boars). All batches tested so far by Q-PCR monitoring have shown negative results for HEV, EMCV, SVDV, PEV9, Rota-A and Reo. In contrast, PPV genome equivalents were detected in multiple lots and ranged from (b) (4) g.e./ gram of DS. PCV1 was detected in 50 lots and ranged from (b) (4) g.e./gram of DS.

PCV2 was detected ranging from [redacted] (b) (4) [redacted] g.e./gram of DS. The lower value presumably reflects the low sensitivity of the assay and not that the virus is not present. Indeed, it is highly likely that these viral geonomes are present in every lot of drug substance. No additional testing for enveloped viruses was performed based on an evaluation of process capability for inactivating these viruses.

Again, the submission did not provide Q-PCR assay validation data for these tests. We sent an information request letter to the DMF holder Nordmark requesting Q-PCR assay validation data. Nordmark sent in a summary (April 29, 2008) in response to our information request. This summary did not provide significant information as to how assays were performed, assay specificity/sensitivity and detection limit, etc.. Therefore I was unable to evaluate their Q-PCR testing results for drug substance. However, given the expected assay sensitivity and the level of viral inactivation demonstrated for enveloped viruses there appears to be a large gap in the ability to control the viral levels in final product. The sponsor should develop more sensitive assays for quantitation of non-enveloped viruses.

Questions

1) Regarding the Q-PCR tests:

   a) Please provide data supporting the validation of the Q- PCR tests used to estimate viral loads of both enveloped and non-enveloped viruses. Please include information on the selection of the primers, assay specificity, sensitivity (LOQ/LOD), linearity and precision, system suitability criteria (including recovery), along with the SOPs for the test protocols.

   b) You have proposed to monitor designated non-enveloped viruses during routine manufacture by the use of a Q-PCR test. However, without validation information on the PCR tests, we are unable to assess your viral testing results. Please provide the validation information and then comment on how this test provides an appropriate level of control for non enveloped viruses.

   c) [redacted] (b) (4)

(b) (4) We therefore recommend that you establish better control of these viruses by setting action limits and specifications for the presence of viral genomes and infectious viruses, respectively.

2) Regarding the viral inactivation studies:

a) According to ICH Q5A, because of the inherent variability of the viral clearance studies, results from two independent evaluations should be performed. However, the viral inactivation studies submitted used material from the same sample in duplicate and not from independent sources. Please provide information on the process's capacity to inactivate viruses from two independent experiments.

b) Please address the huge deviation in results of the FCV spiking study from the two different testing laboratories .

c) Please provide your calculation of the viral genome load for each dose of PEP for all viruses thought to have the capacity to infect humans .

Results of infectivity testing by cell based assays

Infectivity testing for representative DS batches (9 batches) from tissue derived from regular pigs and sows have been investigated for EMCV, Reo, PEV9 and PTV. HEV and Rota-A were not tested due to the inability to culture these viruses. No infectivity for EMCV, Reo, PEV9 and PTV was reported to be detected in the DS. Nordmark analyzed 50 batches of DS for PPV and PCV 1, 2, infectivity . Negative results for infectivity of PCV1 were observed in all 50 batches. Only one batch showed a low titer of infectious PCV2 (at the detection limit of (b) (4) infectious particles/gram of DS). Infectivity by PPV was negative in 15 batches and positive in 35 batches. Infectious particles range from (b) (4) per gram of DS. Among the 35 positive batches, 3 batches contain (b) (4) log, 28 contain (b) (4) log and 4 batches contain (b) (4) logs infectious particles per gram of DS.

In this submission, Nordmark also shows that the data from 11 lots of DS (2007-2008 production) are negative for HEV and PEV9 and positive for PPV genome equivalents. Four lots are negative for PPV infectivity and

seven lots are positive for PPV infectivity with loads ranging from (b) (4) infectious PPV particles/gram of DS. These results are consistent with those of the 50 lots from 2006 production.

HEV genomes were not detected in the product. Currently there is no suitable model virus for HEV and no established in vitro culture system for measuring HEV infectivity. There is a report "development and evaluation of an efficient cell-culture system for HEV" by Tanaka et al. published in the issue of the 2007 March (J Gen Virol). Tanaka observed that HEV RNA was detected in the supernatant of hepatocarcinoma cell line (PLC/PRF/5) inoculated with HEV but there was no obvious cytopathic effect. Serum samples from post HEV infected patients prevented the propagation of HEV in PLC/PRF/5 cells. The author also reported that HEV incubated at temperatures higher than 70 ^{0}C for 10 min was not infectious in PLC/PRF/5 cells, indicating that HEV can be inactivated at temperatures >70 ^{0}C. Theoretically, infectivity of HEV from the pancrelipase final product should also be diminished by the drying step based on the above scientific evidence reported by Tanaka et al. However, the company has not verified these data and the manufacturing process does not appear to effectively inactivate FCV, the presumed, but known flawed model for HEV, as we believe that there is only a 1.6 log reduction for FCV based on the characteristics of this hardy virus and the data from other pancrelipase producers. Thus, it would appear that the contradiction in data reflects the poor modeling of HEV by FCV.

Questions

1. Please provide data supporting the validation of the viral infectivity assays used in the detection of both enveloped and non-enveloped viruses. Please include information on assay specificity, sensitivity (LOD), linearity and precision, system suitability criteria, along with the SOPs for the test protocols.

2. Please provide an estimation of viral load for all viruses thought to have the capacity to infect humans per gram of DS and per dose of PEP for a worst case scenario.

C. Plans for Additional Viral Testing of DS

1. Based on the observations that
   - DS testing (50 lots from production of 2006) for HEV, EMCV, SVDV, Reo, and Rota A were negative

- PPV infectivity was detected in the product
- No significant reduction was found for PEV9 (SVDV) or FCV, Nordmark proposed to perform the following additional testing of 2007-2008 DS lots:

(b) (4)

2. Nordmark will develop a (b) (4)

3. PPV is the only infectious virus that has been reliably detected in most the pancrelipase lots to date. Thus, Nordmark will perform studies on additional treatments leading to reduction of the PPV titre. Based on previous studies, the focus will be on (b) (4)

4. Nordmark will analyze 50 additional lots for HEV and PEV9 (SVDV) genome equivalents as described for PPV. Every lot showing a positive HEV signal will be rejected. Positive PEV9 lot will be investigated for infectivity and in case of a positive result the lot will be rejected. If any of the 50 lots shows a positive PCR signal all future lots will be routinely investigated for genome equivalents of corresponding virus.

Summary of Nordmark's viral testing plan

Nordmark's overall viral testing plan addressed:

(b) (4)

(b) (4)

We disagree with Nordmark's viral testing plan, as it does not sufficiently address risk according to the following:

a) The need to routinely test all viruses thought to have capacity to infect humans when the manufacturing process has not been demonstrated to have excess capacity to inactivate any potential incoming viral load (both non enveloped and enveloped) or that indicate poor health of the source animals with possible impact on product quality.

b) To routinely test infectivity of PCV1 and 2

c) In addition, the program did not address risk mitigation for emerging viruses, animal disease surveillance and sanitizing cleaning procedures for equipment.

Questions

Regarding Item 1:

1. Please clarify that your 50 lots for PPV infectivity testing consist of all lots from one year production or just some of them.
2. We suggest that you routinely test PPV infectivity for all your lots and drop PCR testing since the majority of your lots contain live PPV.
3. Please tighten your PPV infectivity limit to reflect your manufacturing experience. We recommend that no more than (b) (4) logs PPV per gram of DS be allowed in product.

Additional Comments

1. We suggest that you perform routine testing for all viruses thought to have the capacity to infect humans since you cannot quantitate viral loads from the raw material, your manufacturing process may not be able to thoroughly inactivate such viruses, and infection of these viruses in pigs are ubiquitous.
2. Please perform routine monitoring for PCV1 and PCV2 infectivity. The product should be free of PCV1 and 2 infectivity.

IV. Final Comments to be Incorporated to the Letter to Nordmark (MF Holder):

1. You have not provided an adequate description of your risk mitigation plan for adventitious agents. Please provide the following:

   a. Your plan for animal disease surveillance, including how emerging viruses will be assessed and controlled.

   b. A description of the sanitizing/cleaning procedures in place to prevent cross contamination. (b) (4) [redacted]

   c. Please comment on the risk to product quality due to the potential infection of swineherds with parasites.

2. Regarding the viral inactivation studies please address the following concerns:

   a. According to ICH Q5A, because of the inherent variability of the viral clearance studies, results should be obtained from two independent experiments. However, the viral inactivation studies submitted were not performed as recommended, (b) (4) [redacted] Please provide information on the process's capacity to inactivate viruses from two independent experiments.

   b. While you provided two independent results for the spiking experiments using FCV, there is a large difference between the values reported. Furthermore, you provided two calculations of overall FCV inactivation that differed by (b) (4) [redacted] logs without indicating which number you believe best represents process capability. ICH Q5A states that the lower value should be used when evaluating data from independent experiments, which, in this case is consistent with the hardiness of the virus. Please elucidate the reasons for such great differences in inactivation of this virus and consider performing additional studies to get a more consistent evaluation.

c. Although an evaluation of the toxicity or interference of the test sample on the indicator cells appears to have been performed, no data were submitted to support the dilution factors used for the determination of viral titers. Please submit a brief description of the experiments performed and results obtained for the evaluation of assay interference for test samples from the three process steps assessed in the viral evaluation studies.

d. 

e. Please provide a detailed description of the procedures used for the evaluation of the (b) (4) step and include a discussion on the similarity of the (b) (4) process to the commercial process.

3. Regarding the Q-PCR tests:

a. Without adequate information on the validation characteristics of the PCR tests we are unable to fully assess your proposal. Please provide data supporting the validation characteristics of the Q- PCR tests used to estimate viral loads of both enveloped and non-enveloped viruses. Please include information on the selection of the primers, assay specificity, sensitivity (LOQ/LOD), linearity and precision, system suitability criteria (including recovery), along with the SOPs for the test protocols.

4. Regarding the viral infectivity tests:

a. Please provide data supporting the validation characteristics of the viral infectivity assays used in the detection of both enveloped and non-enveloped viruses. Please include information on assay specificity, sensitivity (LOD), linearity and precision. Please submit

the SOPs for the test protocols including a description of the system suitability criteria used to establish the validity of routine test results.

5. Regarding your specifications for adventitious agents:

   a. Please revise your specifications to include routine testing for PPV infectivity for all lots and tighten your acceptance criteria to reflect recent manufacturing history.

   b. While you have proposed to include testing to control the presence of HEV and PEV9, no testing was proposed for EMCV, Reo Virus, and Rota Virus. These viruses are known to cause infection through an oral route and are not inactivated by the manufacturing process, suggesting that better risk mitigation strategies should be employed. Please submit a revised viral testing plan that includes monitoring these non enveloped viruses. Please include a calculation of estimated viral load per dose based on the limit of detection of the Q-PCR assay for HEV, EMCV, SVDV, Rota Virus, and Reo Virus.

   c. Although you plan to measure PPV genome equivalents, we do not believe this information will be useful in establishing a robust correlation between genome equivalents and infectivity and therefore do not consider this study necessary.

   d. Please establish a specification for infectious PCV 1 and PCV 2. We believe that the final product should be free of infectious PCV as your historical data has shown.

   e. Based on the ability of the process to inactivate enveloped viruses, you have proposed not to set specifications for the presence of enveloped viruses. However, we note that it is difficult to validate the absence of adventitious agents, that your control of the procedures followed in the slaughterhouses is very limited and that the limit of detection of viral genomic equivalents may be near the process's capacity to inactivate viruses. Please provide a calculation of estimated enveloped viruses per dose based on the limit of detection of the Q-PCR assay and discuss how your proposal provides an appropriate level of control for enveloped viruses. Given the situation, we believe that setting action limits

and specifications for the presence of viral genomes and infectious viruses, respectively, provides better control of these viruses. Please comment.

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/s/

Maureen Dewey
6/16/2008 10:44:06 AM
CSO
signing for Ennan Guan, Ph.D., Chemist

Amy S Rosenberg
6/16/2008 11:09:48 AM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Center for Drug Evaluation and Research - Food and Drug Administration
Office of Biotechnology Products, Office of Pharmaceutical Science
29 Lincoln Drive, Bethesda, MD 20892

June 3, 2008

NDA:	# 22-210
PRODUCT NAME:	Zentase (EUR-1008)
SUBMISSION DATE:	December 17, 2007
45 DAY FILLING MEETING:	January 31, 2008
FILING DATE:	February 15, 2008
PDUFA GOAL DATE:	June 17, 2008 (Priority Review)
FROM:	Howard Anderson, PhD, Biologist
THROUGH:	Emanuela Lacana, PhD, Associate Chief Laboratory of Chemistry. Gibbes Johnson, PhD, Chief Laboratory of Chemistry Barry Cherney, PhD, Deputy Directory Division of Therapeutic Proteins
SUBJECT:	Review of NDA 22-210 Drug Product
PRODUCT:	Pancreatic Enzyme Product (PEP) Delayed-Release Capsules 5,000, 10,000, 15,000, & 20,000 U USP/capsule
INDICATION:	Exocrine Pancreatic Insufficiency
ROUTE OF ADMIN.	Oral
DOSE REGIMEN:	A EUR-1008 capsule is taken with meals
SPONSOR:	Eurand Pharmaceutical Limited The Yard House Kilruddery Estate Republic of Ireland
CLINICAL DIVISION:	Division of Gastroenterology Products

RECOMMENDATION: Approvable

Eurand should provide information to address the following deficiencies;

1) In section 3.2.P.3.5 you indicate that process validation to the intended full commercial batch size for each manufacturing step will be completed prior to marketing. Please provide a summary of the anticipated validation program. Process validation should be preformed on three consecutive, commercial scale drug product conformance lots. Please indicate when validation studies will be initiated and completed.

2) Please provide detailed information regarding the chemistry, manufacturing and controls for the hydromellose phthalate used for enteric coating of the beads/small beads.

3) The stability data contained in your application are insufficient to support your requested dating period of (b) (4) *years for the drug product. ICH Q5C indicates that expiry dating of products in which the active components are proteins should be set using real time, real temperature stability data. Therefore, the data provided supports an 18 month expiry.*

4) Please specify how long excursions up to 30^{o}C are permitted and provide data to support the excursions.

5) The Nordmark DMF # 7090 has been reviewed in support of NDA # 22-210 and found to contain deficiencies. A letter has been sent to Nordmark listing the deficiencies. Nordmark should address the deficiencies and update the DMF by directly submitting information to the DMF. Please notify the FDA when Nordmark has submitted the requested information.

6) You have not submitted sufficient information in the NDA to evaluate your qualification program for the lipase olive oil substrate. Please provide qualification results for olive oil testing and establish and justify specifications for critical olive oil components.

7) In regards to specifications for release and stability, acceptance criteria should be established based on manufacturing history, process capability and clinical experience. We recommend that:

> *a) You tighten acceptance criteria for the protease and amylase activity to reflect actual manufacturing capability, for both final and intermediate drug product.*

c) Please establish a release specification for Phthalic Acid (FPA) for the 4 Drug Product strengths, and provide a justification for the acceptance criteria chosen.

d) Acceptance criteria for the Uniformity of Dosage Units should be the same for the clinical/stability lots and for the lots to be marketed. The proposed weight limit of (b) (4) *of target fill weight is too broad to ensure consistent manufacturing of EUR-1008. Please revise the acceptance criteria accordingly.*

e) Please establish and justify a specification for water content for drug product release and stability testing.

8) As part of the RP-HPLC assay validation, please determine how much protein is retained on the column.

9) The certificate of analysis for the RP-HPLC pancrelipase reference standard release testing only includes specifications for peak areas. Please develop a rigorous qualification program aimed at ensuring that the quality attributes of the internal reference standard are maintained when new internal reference standards are required and manufactured. We also recommend that an internal reference standard that reflects the commercial manufacturing process be used, in addition to the pancrelipase drug substance reference standard, in all release and stability testing.

10) The working standard certificate of analysis for batch # P13309305 has two different USP lipase specific activities depending on the USP reference standard used. Please develop and implement a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the reference standard.

DMF References and background:

Letters of Authorization have been provided for the following DMFs

DMF 7090 (BULK DRUG SUBSTANCE)

DMF (b) (4)
DMF (b) (4)
DMF (b) (4) **(**
DMF (b) (4) **(**
DMF (b) (4) **(**
DMF (b) (4) **(**
DMF (b) (4)
DMF (b) (4) **(**
DMF (b) (4) **(**
DMF (b) (4) **(**

(b) (4)

S. Drug Substance

The review of the Drug Substance is provided in Dr. Anderson's review of DMF 7090 (Nordmark – Pancrelipase)

(b) (4)

P DRUG PRODUCT

P.1 Description and Composition of the Drug Product

EUR-1008 Hydromelose capsules contain 5,000, 10,000, 15,000 & 20,000 USP Units Lipase. Capsules contain enteric coated pancrelipase formulated with compendial excipients. The 10 K, 15K, & 20K U USP EUR-1008 strengths contain identical pancrelipase formulated beads. The 5 K strength beads ("small coated bead") are prepared with approximately dose-proportional pancrelipase and excipients. The 10 K, 15 K, & 20 K capsules contain enteric coated cylindrical mini-tablets having a diameter of (b) (4) mm and a thickness of 2.2 mm. The 5K capsules contain slightly smaller mini-tablets having a diameter of (b) (4) mm and a thickness of (b) (4) mm.

	Description		
Strength USP Unites (Lipase)	**Capsule Size**	**Capsule Label**	**Capsule Color**
5,000	4	Eurand 5	White Cap, White Body
10,000	2	Eurand 10	Yellow Cap, White Body
15,000	0	Eurand 15	Red Cap, White Body
20,000	0	Eurand 20	Green Cap, White Body

EUR-1008 tablets are enteric coated to avoid destruction in the acidic stomach environment and are released in the upper small intestine duodenum. Excipients were

chosen based on favorable disintegration rates. Hypromellose phthalate (HPMCP) is commonly used in oral pharmaceutical formulation since it is insoluble in gastric fluids and will swell and dissolve in the upper intestine. (b) (4) All EUR 1008 excipients are compendial grade (except FDA C Blue 2(21 CFR compliant)).

EUR 1008 Packing and Strengths

(b) (4)

P.2.2 Pharmaceutical Development

P. 2.2.1 Components of the Drug Product

Excipient	**Function**
Core Beads	
Croscarmellose Sodium	
Hydrogenated Castor Oil	
Colloidal Silicon Dioxide	
Mycrocrystalline Cellulose	
Magnesium Stearate	
Coating	
Hypromellose Phthalate	
Talc	
Triethyl Citrate	
(b) (4)	
Hard Capsules (HPMC), Various Sizes	

(b) (4)

P.2.2.1 Formulation Development

Eurand has been manufacturing delayed release pancreatic enzyme products for

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/s/

Howard A Anderson
6/4/2008 03:05:32 PM
CHEMIST

Gibbes R Johnson
6/4/2008 05:59:29 PM
CHEMIST

Barry Cherney
6/5/2008 02:21:15 PM
CHEMIST

ONDQA Pre-Marketing Assessment Division II
Branch III
NDA Consultation - Quality Assessment

1. NDA number: 22-210

2. OND Division: HFD-180

3. Applicant Name and Address:

Eurand Pharmaceuticals Limited
The Yard House
Kilruddery Estate
Southern Cross Road
Bray Co. Wicklow
Republic of Ireland

4. Drug Reviewed: Zentase (EUR-1008)

5. Purpose of Consultation: To review the dissolution study of the drug product.

6. Summary: The analytical procedures used for dissolution, dissolution acceptance criteria for the drug product, and stability results for dissolution were reviewed. The methods, standard materials, and control of the drug product dissolution in the NDA 22-210 were found ADEQUATE and support the proposed 18 months expiration date.

Bogdan Kurtyka, Ph.D.
Review Chemist, Branch III
Premarketing Assessment Division II
ONDQA

Date

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Premarketing Assessment Division II
ONDQA

Date

Review notes

The drug product EUR-1008 consists of a capsule filled with delayed release beads (enteric coated) containing Pancrelipase USP. Four strengths are proposed – 5,000; 10,000; 15,000; and 20,000 USP Units Lipase.

The current review deals with all parts of NDA 22-210 related to dissolution as follows:

- analytical procedures used for dissolution,
- reference standards,
- acceptance criteria for dissolution in the drug product specification,
- conformance of registration batches to specification on release, and
- stability results for dissolution

The analytical procedure for dissolution follows the method outlined in the USP monograph on Pancrelipase Delayed-Release Capsules. In order to measure lipase activity, the applicant uses (b) (4) instead of USP Bile Salts RS described in the USP monograph. This deviation from the USP procedure is considered minor.
It is noted that for the calculation of the lipase activity after (b) (4) of dissolution in the phosphate buffer, a correction factor of (b) (4) is used to compensate for the lipase loss of activity over the period of 30 minutes in the buffer at 37°C. The value of the correction factor is supported by data documented in the method validation. ACCEPTABLE.

The application lists two main reference standards that can be used in dissolution studies. The primary standard is the USP Pancreatin Lipase RS. The application includes the USP Certificate for Pancreatin Lipase RS Lot 1.
For routine testing of lipase activity working standards are normally used. The application provides Certificates of Analysis of 5 batches of working standard of Pancrelipase, all qualified against USP primary standard. ACCEPTABLE.

The drug product specification proposes a limit of NLT (b) (4) in (b) (4) for dissolution. This limit is consistent with the USP monograph on Pancrelipase Delayed-Release Capsules. The application does not include multiple-point dissolution curves that normally are the basis for establishing the dissolution acceptance criteria. However, in the case of this delayed release drug product, the faster dissolution (e.g., (b) (4)) would not compromise the safety and efficacy of the drug. The drug acts locally by helping to digest fats, starches, and protein, and is not systemically absorbed. Therefore its increased levels would not create safety hazards. ACCEPTABLE.

The application includes batch analysis data for all clinical/stability bulk drug product batches and packaged drug product batches manufactured in support of the NDA, a total of 12 batches. All batches show dissolution results above limit. ACCEPTABLE.

Formal stability studies were performed using the proposed commercial container/closure system. Twelve months data at long term conditions and 6 months data at accelerated conditions are provided in the application. The applicant proposes 18 months of tentative shelf life.
No significant changes in dissolution occurred during the study. Although the long term dissolution data show some variability over time, the review of the data confirms that the proposed shelf life of 18 months is ACCEPTABLE based on dissolution results.

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/s/

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