

Viral Safety Issues for the Pancreatic Enzyme Product CREON

Barry Cherney, Ph.D.

Deputy Director,

Division of Therapeutic Proteins,
OBP/OPS/CDER

Overview

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- II. Introduction to Viral Issues
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Pancreatic Enzyme Product Guidance Regarding Product Quality

- Guidance For Industry: Exocrine Pancreatic Insufficiency Drug Products - Submitting NDAs (April 2006)
- Recommendations for improved assurance of product quality/consistency
 - Control of Manufacturing
 - Stricter adherence to CGMP: identification of critical process steps
 - Establishment of in-process controls such as well defined process times
 - Better Physicochemical/Biological Characterization of Drug Substance
 - Release Testing
 - Formal assay validation in accordance with FDA and international guidance
 - Stability and Overages
 - Potency (Lipase Units) must reflect the label claim: overages to compensate for loss during storage are not permissible

II. Introduction to Viral Issues

Viral Considerations

- Viral issues were not explicitly identified as product safety/quality issues when FDA ruled that PEPs should be available by prescription only (FR, April 2004)
- Historically, most PEP manufacturers have neither monitored viruses nor evaluated the manufacturing process for viral inactivation, presumably because of the lack of perceived risk:
 - Oral administration of food grade product: presumed safety, but also the route of transmission by some viruses
 - Process has some potential to inactivate viruses
 - Long history of “safety” regarding viral infections. No documentation of transmission of an infectious disease despite very extensive use and multiple manufacturers.

However:

- Risk of transmitting disease from animal based drugs appears to be low but valid. Swine populations are infected with known and perhaps unidentified 5 viruses.

Viral Considerations

- General Risk Considerations:
 - Pork is usually cooked (170°F/ 77°C) or cured, reducing viral load by some measure; viral load in muscle tissue versus pancreatic tissue is unknown..
 - CREON is designed to be released in the small intestine: bypasses low pH environment of stomach which inactivates some but not all viruses
 - Intensity of exposure: chronic use of product, chronic viral exposure. A patient with a body weight of 60 Kg (i.e., 132 lbs) could receive up to 3.75 grams of pancrelipase daily
 - In the past, there was no requirement for reporting adverse events pertaining to PEPs to the FDA. Additionally, some patient populations using PEPs have high background rate of infections so it may be difficult to discern infectious disease events related to the use of the product.

NY Times Article (April 1, 2008)

“Seeking Alternatives to Animal Derived Drugs”

- PEP supplier stated that “the enzymes carried a pig virus that is not dangerous to humans and that eliminating all viruses from the pills could result in damage to the enzymes”
- Article raised “possibility that unidentified viruses or other contaminants could threaten supplies of the drug” (i.e., PEP)
- “In 2006 the F.D.A. said that the viruses must nonetheless be eliminated or rendered inactive” – We believe this statement was taken out of context

FDA PEP Guidance (April 2006): Recommendation for a Full Viral Risk Assessment

- Guidance For Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs (April 2006)
 - “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).**
 - Q5A Sets a very high standard
 - The best reasonable assurance that the product is **free of virus contamination**
 - Requires knowledge of how much virus may be present in starting materials and validated viral test methods

ICH Q5A Strategies for Control of Adventitious Viruses in Cell Line Based Protein Therapeutics

- A comprehensive control strategy
 - Animal/tissue source screening, if primary cell cultures
 - Rigorous cell bank screening for viruses
 - Demonstration of viral clearance/inactivation by multiple robust orthogonal process steps
 - Excess capacity to clear viruses
 - Routine screening of cell culture harvest

FDA's Approach

- ICH Q5A was meant for parenteral products, mostly of recombinant origin, not for orally administered or animal derived materials
- Sound science and risk evaluations should be applied. Apply ICH Q5A as appropriate
- Apply reasonable practices that minimize the risk to patient safety while ensuring that efficacious products *are available*
- We seek expert guidance from this committee on the “best” approaches – a reality check.

III. Viral Risk Assessments

Risk

- Risk can be defined as the combination of
 - the probability of occurrence of *harm* and
 - the *severity* of that harm
- Risk to patients, care givers and society
- Testing & a well designed manufacturing process can reduce risk of occurrence
- Risk must be viewed in the context of benefit: clear benefit versus potential risk of uncertain magnitude
- Assessment of the magnitude of the risk is what FDA seeks from this Committee

Risk Assessment for PEPs

The viral risk assessment should include evaluation of the following:

1. Control of source material
 2. Potential of viral species as human pathogens
 3. Potential input viral loads (discussed in the closed session)
 4. The capacity of the process to remove or inactivate model or relevant viruses (discussed in the closed session)
 5. The impact route of administration has on viral safety
- Note that risk assessment did not emphasize the risks of ***unknown viruses*** that might infect human populations, but could be evaluated using indicator cell lines and animal testing

1. Source Materials: Limited Control for PEPs

- Pigs From: US/Europe
- Pancreas glands derived from pigs raised and slaughtered for food. No other species are slaughtered and processed at each facility.
- Slaughterhouses are regulated under the auspices of the USDA and European authorities. Regulations for slaughterhouses focus on animal hygiene, source, veterinary records (health certification of the animals), **surveillance of herds**, and documentation of feeds.
- Good Manufacturing Practices (GMPs) for Drugs are not followed.
- Organ quality is monitored by visual inspection at receiving by a product specialist.
- Vaccination of pigs for PCV-2 and breeding sows for PPV in some locations, primarily USA

2. Risk Identification:

Enveloped Viruses Found in Swine Tissues

- Pseudorabiesvirus
- Influenza A
- Vesicular Stomatitis Virus
- Rabies Virus
- African Swine Fever Virus
- Transmissible Gastroenteritis Virus
- Classical Swine Fever Virus
- West Nile Virus
- Suipoxvirus
- Hantavirus
- Porcine Cytomegalovirus
- Porcine Lymphotropic Herpesvirus
- Porcine Endogenous Retrovirus
- Porcine Respiratory Reproductive Syndrome Virus
- Paramyxovirus
- Encephalomyelitis Virus

2. Risk Identification:

Non-Enveloped Viruses Found in Swine Tissues

- Swine Hepatitis Virus
- Encephalomyocarditis Virus
- Swine Vesicular Disease Virus
- Porcine Rota Virus
- Reovirus
- Foot and Mouth Disease Virus
- Porcine Teschovirus 1
- Vesicular Exanthema Virus
- Porcine Adenovirus
- Porcine Respiratory Coronavirus
- Porcine Parvovirus
- Porcine Circovirus 1 and 2

2. Risk Identification: Swine Viruses that are Known Human Pathogens

Enveloped	Primary Route of Transmission	Estimated Occurrence
Influenza A	Respiratory	very low
Paramyxovirus (Nipah & Menagel Virus)	Oronasal	very low
Vesicular Stomatitis Virus	Respiratory	very low
Pseudorabiesvirus	inoculation	low
Rabies Virus	inoculation	low
West Nile Virus	inoculation	low
Hantavirus	inoculation	low
Eastern Equine Encephalomyelitis Virus	inoculation	low
Non-Enveloped		
Swine Hepatitis E Virus	Oral	medium
Encephalomyocarditis Virus	Oral	low
Swine Vesicular Disease Virus	Oral	low
Porcine Rota Virus	Respiratory	medium
Foot and Mouth Disease Virus	Oral	very low
Reovirus	Oral	medium

Occurrence reflects frequency in swine population, detectability of disease and target tissue tropism

2. Risk Identification

Swine Viruses: Not Known Human Pathogens

a. Unknown Swine Pathogens

- An active animal disease surveillance program
- In vitro/ In vivo adventitious agent tests are capable of detecting these types of viruses

b. Swine Pathogens not known to infect humans but ubiquitous in pigs and may be present in drug product

- Non-enveloped viruses: Porcine Parvovirus (PPV) and Porcine Circovirus 1 & 2 (PCV 1 & 2)
- Reason for risk: potential to change species tropism

Risk Assessment:
Infectious Porcine Parvovirus and
Porcine Circovirus

Considerations Regarding PPV in PEPs

- Most swine herds have been infected with PPV
- Parvoviruses are extremely resistant to physicochemical treatment, withstand 100°C for 30 min
- May not be feasible to revise the manufacturing process to achieve a more robust level of inactivation/clearance without compromising product quality
- Elimination of contaminated lots by testing could result in failure of some to many lots

Infectivity of PPV in Humans & Lower Animals

- Porcine parvovirus generally has not been found to infect human cells, but one viral strain infected some stable human cell lines (Hallauer, et. al. 1977. Archiv fur die Gesamte Virusforschung)
- Pig farm workers (N=56) who had close daily contact with PPV infected pigs for one year or greater were not positive for PPV antibodies (Wattanavijarn, W., et al., 1985. Trans R Soc Trop Med Hyg 79:561)
- Consumers of pork products may be exposed to live virus, but meat may have a different viral load. Consumption of pork products is not associated with known disease from PPV but true impact has not been thoroughly investigated.

However

- Feline PV has crossed species barrier to infect dogs and resulted in the deaths of many dogs (Hueffer 2003. Current Opinion in Microbiology)
- Lack of studies evaluating presence of antibodies to PPV in patients with CF using PEPs. FDA is engaged in a study to screen patients with CF on long term PEP therapy for antibodies to PPV or PCV-2 to better assess risk to patients.

PPV Severity

- PPV in swine is pathogenic in pregnant sows
- Potential pathogenicity of PPV in humans is unclear i.e., unclear what would constitute human disease manifestations, but a change in species tropism is of great concern

Porcine Circovirus Considerations

- PCV-2 is associated with a debilitating disease referred to as post-weaning multisystemic wasting syndrome.
- Porcine Circoviruses are resistant to physico-chemical treatment and live virus could be expected to be present in drug product depending on the specific manufacturing process
- Oral/nasal route is believed to be the route of infection
- PCV has been shown to infect human cell lines but mixed results have been reported for evidence of PCV-2 infection in humans (Hattermann et. al., 2004. Xenotransplantation 11: 284-294.)
 - Antibodies to PCV were reported in 30% of samples from hospitalized patients with fever of unknown etiology but results have not been confirmed (Tischer, et. al., 1995. Arch Virol 140: 1427-1439)
- PCV-2 may have potential as a zoonotic agent because it produces persistent infections, is vertically transmitted and shows some genetic variability which raises issues regarding the ability to change species tropism (Parrish et. al., 2008. Micro & Mol Biol. Rev. p 457-470)

Realities of Cross-Species Infections

- SIV counterparts of HIV-1 & HIV-2 were introduced into human populations at least 7 times
- Majority of human pandemic arose from 1 cross-species infection (HIV-1 group M viruses)
- Recombination between distinct viral lineages co-infecting a single animal are not rare events in nature
- Recombination leads to altered tropism, virulence and drug resistance patterns
- Other examples from Swine
 - Influenza
 - Nipah virus (from bats to humans sometimes via swine)

Risk versus Benefit: FDA Management of Parvovirus Risk

Case studies illustrate regulatory approaches
toward Parvoviruses:

Human parvovirus B19

Minute Virus of Mouse

Human Parvovirus B19 Pathogenicity

- Commonly causes **fifth disease** (erythema infectiosum) a self-limited disease of children. Non-immune adults may develop rash and/or joint pain
- May cause **transient aplastic crisis (TAC)** in persons with sickle-cell anemia
- Occasionally causes serious complications during **pregnancy** (e.g. abortion, fetal anemia, hydrops fetalis)

Risk Due to Parvovirus B19 in Human Blood Products

- A high percentage of the human population has been infected with B19. Rejection of blood units based on a screening test could eliminate a large % of donors.
- Screening of blood donations for the presence of B19 is currently not routine – accept risk based on benefit and difficulty in mitigating risk any further.
- Source plasma is screened for B19 and manufacturers have placed a limit of $< 10^4$ genomic equivalents based on information indicating that lower inocula have greatly reduced risk of infections

Conclusion: We tolerate a relatively high level of risk for B19, a known human pathogen because risk cannot be mitigated further without loss of blood supply. Benefit outweighs the risk.

Risk Associated with Minute Virus of Mouse

- Parvovirus that infects Chinese Hamster Ovary (CHO) cells commonly used to produce recombinant proteins
- No known pathogenicity in humans
- Viewed as a contaminant that can be well controlled
- MVM not tolerated in production streams: recently caused a shut down in production for 2 months of one biotech product
- No drug shortage occurred as a result of this control strategy for this product

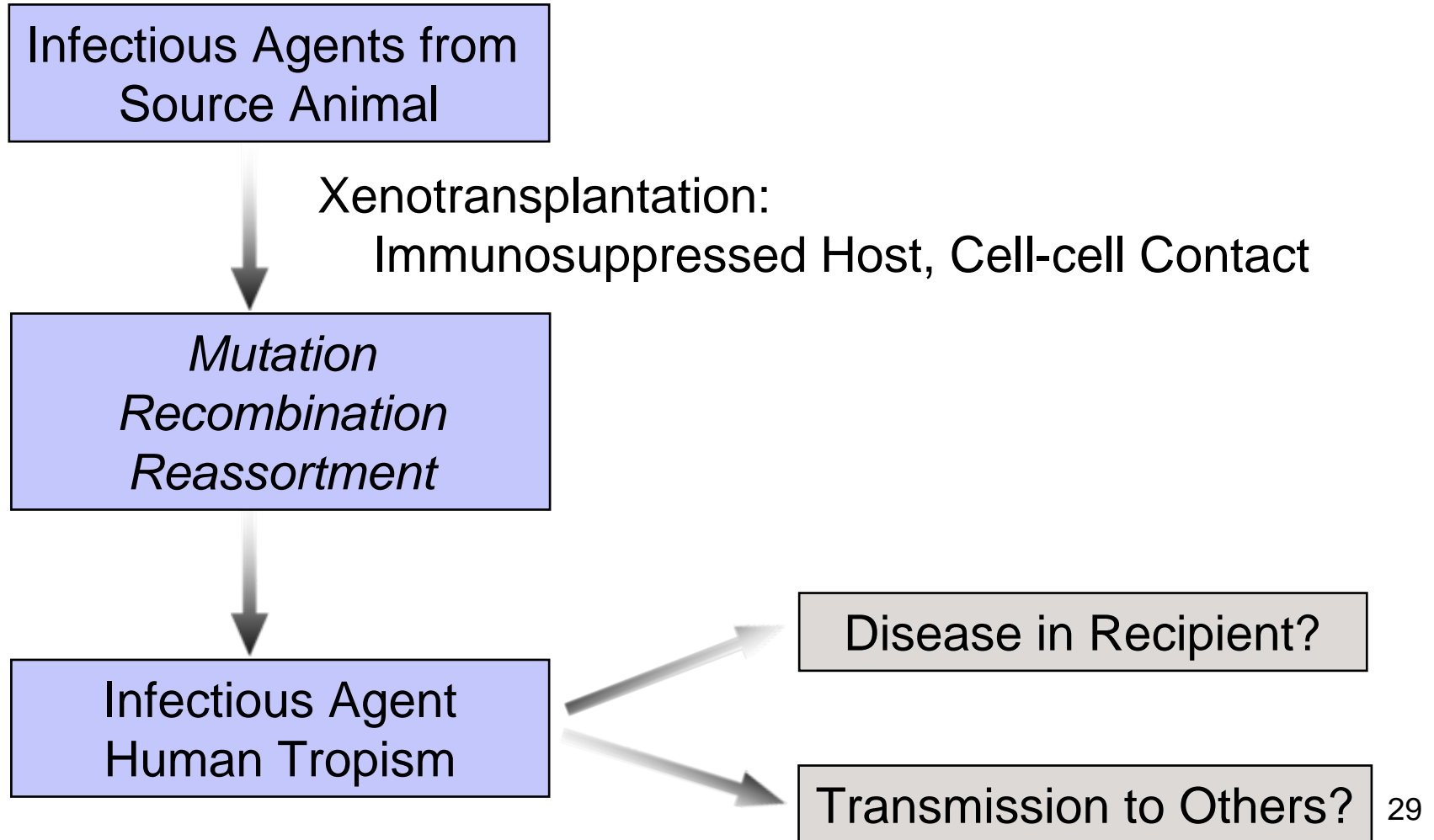
Conclusion:

Theoretical risk can be reduced to very small levels with appropriate controls with no impact to product availability in some cases

Overall Conclusion:

We accept a wide range of risk, based in large part on the ability to mitigate the risk to minimize the *impact* on public health

Xenotransplantation Raises Public Health Concerns



Risk Mitigation for Xenotransplantation

For Source Animals

- Stringent requirements for source animals and product testing
 - Establish source animal facility barriers to limit lifelong exposure of source animals; closed herds
 - Infectious disease screening of herd and source animals
 - Product specific testing: depends on source species, tissue types, geographically emerging viruses

For Recipients

- Informed consent, education and counseling
- Surveillance of all patients: use of diagnostic assays; specimen/serum banking
- Maintenance of health care records

4. Risk Assessments

- Studies to determine the capacity of the manufacturing process to remove or inactivate viruses were performed in accordance with FDA guidance
 - 2 robust viral clearance steps have been shown
 - The studies show that the manufacturing process for pancrelipase can inactivate enveloped viruses but the process does not inactivate all non-enveloped viruses and shows moderate to limited inactivation for these viruses
 - These studies suggest that testing strategies should be employed to reduce the risk to product quality, particularly regarding certain non-enveloped viruses

Risk Mitigation Strategy

- The manufacturing process should have excess capacity to remove enveloped viruses. Therefore studies were performed to assess the potential initial enveloped viral loads and raised issues as to significant safety margins and requirements for additional testing for enveloped viruses. This issue was discussed in detail within the closed session and expert advice provided to the FDA.
- Because certain viruses of demonstrated zoonotic potential are not effectively inactivated by the process, Solvay Pharmaceuticals has established a testing strategy for zoonotic viruses in situations where the potential contamination of the source material can not be excluded or where the ability of the process to inactivate the virus cannot be assured with a high degree of confidence. Drug substance is routinely tested for these non-enveloped viruses with rejection of positive batches. Details were discussed within the closed session and expert advice provided to the FDA.

Risk Mitigation Strategy for Swine Viruses that are not Known Human Pathogens

- PPV, PCV 1 and 2 are not effectively inactivated by the process and live virus is likely to be present in some doses of pancrelipase
- Risk associated with potential infections with PPV or PCV appears to be very low. This risk could be further reduced by:
 - Testing for infectivity thus limiting patient exposure
 - Routine surveillance and monitoring for zoonotic events in patients treated with pancrelipase
 - Better understanding of the risk by conducting appropriate studies elucidating the potential for transmission to humans

Risk Mitigation: Better informed Patients and Caregivers

- Provide information to care givers and patient on risks, for example:

WARNINGS Product Source

This product is sourced from pancreatic tissue from swine used for food consumption. Although the risk that CREON® will transmit an infectious agent to humans has been reduced by testing for certain viruses during manufacturing and by inactivating certain viruses during manufacturing, there is a theoretical risk for transmission of viral disease including diseases caused by novel or unidentified viruses. Thus, the presence of porcine viruses that might infect humans cannot be definitively excluded. In addition, porcine parvovirus which has not been documented to infect humans may be present in pancreatic enzyme products. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported.

- Provide instructions if an infection is observed that might be related to the product, for example:

All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to