DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE MEETING

OPEN SESSION

Tuesday, December 2, 2008

12:00 p.m.

Hilton Washington, D.C./Silver Spring
8727 Colesville Road
Silver Spring, MD

C O N T E N T S

C O N T E N T S (Continued)

PARTICIPANTS:

Ian McGowan, M.D., Ph.D., FRCP, Chair
Paul Tran, RPh, Designated Federal Official

ANTIVIRAL DRUGS ADVISORY COMMITTEE (AVDAC) (Voting)

Ian M. McGowan, M.D., Ph.D., FRCP
Patrick G. Clay, Pharm.D.
Marshall J. Glesby, M.D., Ph.D.
Peter L. Havens, M.D.
Amneris E. Luque, M.D.

ANTIVIRAL DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)

Joseph S. Camardo, M.D. (Industry Representative)

ARTHRITIS ADVISORY COMMITTEE MEMBER (Voting)

Diane D. Aronson, B.S. (Consumer Representative)

CENTER FOR DRUG EVALUATION AND RESEARCH TEMPORARY VOTING MEMBERS (Voting)

John P. Burke III (Patient Representative)
George D. Ferry, M.D., FAAP
Carolyn M. Kercsmar, M.D.
Colin R. Parrish, Ph.D.

REGULAR GOVERNMENT EMPLOYEES (Voting)

Larry J. Anderson, M.D.
Gregory L. Armstrong, M.D.
CAPT Louisa E. Chapman, M.D., MSPH
Milica S. Chernick, M.D.
Walid Heneine, Ph.D.
Eileen L. Thacker, D.V.M., Ph.D., DACVM

FDA PARTICIPANTS (Non-Voting)

Julie Beitz, M.D.
Amy Rosenberg, M.D.
Anne Pariser, M.D.
Ethan Hausman, M.D.
Barry Cherney, Ph.D.

P R O C E E D I N G S

Call to Order

DR. McGOWAN: Good afternoon. Welcome to the Open Session of the Antiviral Drugs Advisory Committee. To begin, I have a statement to read.

"For topics such as those being discussed at today's meeting, there are often a variety of opinions some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

"Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair and we look forward to a productive meeting.

"In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee Members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting

with the media until its conclusion. A press conference will be held in the Potomac Room immediately following the meeting today.

I would also like to identify the FDA press contact, Ms. Rita Chapelle. Is she here? She is waving at the back. So, that is your contact for the FDA.

I would also like to remind everyone, please, to silence your cell phones, beepers and other electronic devices if you have not already done so.

The committee is also reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you very much.

I would now like the committee to introduce themselves and maybe we could begin with Dr. Julie Beitz, on my left, and work around the table.

Introduction of Committee

DR. BEITZ: My name is Julie Beitz. I am the Director of Office of Drug Evaluation III.

DR. ROSENBERG: Amy Rosenberg, Director of Division of Therapeutic Proteins.

DR. PARISER: Anne Pariser, Medical Team Leader, Division of Gastroenterology Products.

DR. CHERNEY: Barry Cherney, Deputy Director, Division of Therapeutic Proteins.

DR HAUSMAN: Ethan Hausman, Clinical Reviewer, Division of Gastroenterology Products.

DR. FERRY: George Ferry, Professor of Pediatrics at Baylor College of Medicine in Houston.

DR. PARRISH: Colin Parrish, Professor of Virology at Cornell University in Ithaca.

DR. CHERNICK: Milica Chernick, physician at NIDDK, NIH.

MS. ARONSON: Diane Aronson, Consumer Representative.

DR. HAVENS: Peter Havens, Pediatric Infectious Diseases at the Medical College of Wisconsin and Children's Hospital of Wisconsin in Milwaukee, Wisconsin.

DR. GLESBY: Marshall Glesby, Adult Infectious Diseases, Cornell Medical College.

DR. McGOWAN: Ian McGowan. I am a Professor of Medicine at the University of Pittsburgh, School of Medicine.

MR. TRAN: Paul Tran, Designated Federal Official

for the Antivirals.

DR. CLAY: Patrick Clay, Pharmacist, Kansas City, Missouri.

DR. LUQUE: I am Amneris Luque, Adult Infectious Diseases, University of Rochester Medical Center.

MR. BURKE: John Burke, Patient Representative.

DR. KERCSMAR: Carolyn Kercsmar, Pediatric Pulmonologist, Professor of Pediatrics, Cincinnati Children's Hospital.

CAPT CHAPMAN: Louisa Chapman. I am an infectious disease physician and a viral epidemiologist at the Center for Disease Control and Prevention.

DR. HENEINE: Walid Heneine, HIV Laboratory, Division of HIV-AIDS Prevention, CDC.

DR. THACKER: Eileen Thacker, USDA-ARS National Program Leader, Animal Health.

DR. ARMSTRONG: Greg Armstrong. I am an adult infectious disease physician and medical epidemiologist at CDC.

DR. ANDERSON: Larry Anderson, Division of Viral Diseases, National Center for Respiratory and Immunization

Diseases, CDC.

DR. CAMARDO: Joseph Camardo. I am head of Medical Affairs at Wyeth Pharmaceuticals.

DR. McGOWAN: Thanks very much, everyone.

I would now like to pass it over to Paul Tran who is our Designated Federal Official, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

MR. TRAN: Good morning. The Food and Drug Administration is convening today's meeting of the Antiviral Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with the Federal ethics and conflict of interest laws covered by, but not limited to, those found in 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to

participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with the Federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees with potential financial conflicts when necessary to afford the committee the essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments,

consulting, expert witness testimony, contracts, grants, teaching, speaking, writing, patents and royalties and primary employment.

For today's agenda, the Committee will discuss the safety and efficacy of New Drug Application 20-725, Creon (pancrelipase delayed-release capsules) for the treatment of exocrine pancreatic insufficiency.

This is a particular matter meeting during which the specific matters related to Solvay's Creon will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

With respect to the FDA invited industry representative, we would like to disclose that Dr. Joseph Camardo is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Camardo's role at this meeting is to represent industry in general and not any particular company.

Dr. Camardo is employed by Wyeth Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant will need to exclude themself from such involvement of the exclusion and will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue.

Thank you.

DR. McGOWAN: Thanks very much, Paul.

We will now proceed with Opening Remarks. I would like to invite Anne Pariser from the Division of Gastroenterology Products, to provide us with her opening remarks.

Thank you.

Opening Remarks

DR. PARISER: Thank you. I will be very brief. I just wanted to welcome everybody now to the open portion of this advisory committee, welcome again to the committee members but also to members of the public. Just to restate

for the open session that the purpose is to discuss the theoretical risk of porcine viruses known to be present in the PEPs 2 patients versus the known medical benefits of these products.

I just wanted to remind everybody that now that we are in the open session, just caution everybody to be aware not to mention any specific manufacturing process information which is trade secret information.

Thank you.

DR. McGOWAN: Thanks very much, Anne.

We will now proceed to the sponsor presentation, which is Solvay Pharmaceuticals. I would remind the team from Solvay they have an hour to make their presentation. We are running a little late so, if they could keep within the time constraints, that would be great.

I would also like to remind public observers at the meeting that whilst this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Thank you.

Presentations from Sponsor

Introduction

DR. RACZKOWSKI: Good morning, Dr. McGowan, panel members, representatives of FDA, ladies and gentlemen.

[Slide.]

It is our privilege today to be here on behalf of Solvay Pharmaceuticals to present to you our product Creon or Pancrelipase Delayed Release Capsules.

[Slide.]

My name is Victor Raczkowski and I am Vice President of Regulatory Affairs in the U.S. at Solvay.

[Slide.]

We have proposed that Creon be indicated for the treatment of patients with maldigestion due to exocrine pancreatic insufficiency.

[Slide.]

After my introduction, Dr. Virginia Stallings of Children's Hospital of Philadelphia will describe the medical need for pancreatic enzyme products such as Creon, and both FDA and Solvay share the view that pancreatic enzyme products are medically necessary to the well-being of patients with exocrine pancreatic insufficiency.

Dr. Earl Sands, of Solvay, will then present clinical efficacy and safety data supporting the approval of

our product and, because products in this class like Creon are derived from swine, Dr. X.J. Meng, of the College of Veterinary Medicine at Virginia Polytechnic Institute, will provide an assessment of the risk of human infection from porcine viruses. Dr. Meng is the discoverer of the swine hepatitis E virus.

Finally, Dr. Sands will return to describe Solvay's proposal for a proactive surveillance program to monitor for the clinical presence of viral infections. Our program identified strategies for viral risk identification and evaluation that Solvay, as a leader in this class, could implement.

[Slide.]

We hope that the information we provide you today will allow you to make a thorough evaluation of both the benefits and risks of Creon, as well as to give you a better understanding of the issues surrounding viral safety in this product class.

The pancreatic exocrine insufficiency, abbreviated here as EPI, is inability to properly digest food due to a lack of digestive enzymes made by the pancreas. The enzymes fall into three major enzyme classes and in the intestine,

they digest or break down fats, proteins and carbohydrates into smaller nutrients that can be absorbed by the body.

Exocrine pancreatic insufficiency is a comorbidity of several serious conditions including cystic fibrosis, chronic pancreatitis and other conditions.

It also results from procedures such as pancreatectomy or surgical resection of a patient's pancreas and, for patients with this condition, pancreatic enzyme replacement therapy, or PERT, is essential for adequate nutrition. Without it, the impaired digestive process can lead to chronic malnutrition and, in infants and children, can result in failure to thrive, delayed development and stunting of growth.

[Slide.]

Now, clearly, as Dr. Stallings will describe in more detail, good nutrition is a vital component of treatment for patients with EPI. For these patients, no treatment is simply not an option.

As I will explain on the next slide, there currently are no FDA-approved pancreatic enzyme treatments available and we are proud at Solvay with Creon to be the first to reach this step in the approval process and also to

be the first to be engaged in this public dialogue.

[Slide.]

Pancreatic enzyme products existed before the Federal Food, Drug and Cosmetic Act of 1938 was passed. Therefore, our products in this class that currently are being marketed in the United States have never been formally approved by the FDA.

Solvay has over 100 years of experience with pancreatic enzyme products. Our currently marketed product, or CMP, has been available since 1993 and, because Creon has been approved in 75 countries although not in the United States, Solvay does submit periodic safety update reports to regulatory authorities, and Solvay has approximately 5 million patient years of experience with Creon.

In 2004, FDA passed a regulation requiring that all pancreatic enzyme products undergo formal regulatory approval and at Solvay, we have used this as an opportunity to what we call the "to-be marketed product," or TbMP, for which we are now seeking FDA approval.

Our to be marketed product is a refined version of the currently marketed product. It includes an active ingredient pancrelipase that is manufactured by Solvay, and

this active ingredient has about 15 years of established use in our European Creon product.

In addition, the Creon formulation has been modified and adjusted to meet current regulatory requirements.

[Slide.]

Dr. Sands will describe our clinical and efficacy data for Creon and he will describe the results of a clinical efficacy study, No. 3126 in patients with cystic fibrosis, that FDA requested that we perform as part of the approval process.

This study demonstrated improvements in the primary endpoint, the Coefficient of Fat Absorption. Creon also improved symptoms of EPI.

The efficacy results from this study were entirely consistent with pooled Creon efficacy data from studies conducted with Creon over the last 20 years.

[Slide.]

In clinical experience, Creon has generally been safe and well tolerated. Clinical trial experience with Creon, which includes study 3126, exceeds 1,500 patients, and this is the largest clinical trial database in the world

for any pancreatic enzyme product.

Postmarketing experience with Creon is approximately 5 million patient years, and the most common adverse experiences are listed here.

In both clinical trial and postmarketing experience, there has been no pattern of viral illness or conditions.

[Slide.]

As described in detail this morning in the closed session, Solvay has a robust system for reducing viral loads during the manufacturing of Creon, and Solvay's system includes careful sourcing of pancreatic glands, viral inactivation in the manufacturing steps and release testing of the product before it reaches patients.

In the manufacturing process, we have shown that enveloped viruses are effectively inactivated and that the realistic risks from non-enveloped viruses is low.

[Slide.]

On the clinical side, Dr. Sands will describe an additional proposal for viral identification and evaluation. There are three key aspects to this proposal.

First, retrospective analyses using both U.S. and

UK databases. Second, prospective observation and evaluation of patients including active surveillance and the use of sentinel sites to collect biomaterial for viral assessment. Third, proposing elements to include in labeling for all products in this class.

[Slide.]

In conclusion, there are several key themes we would like to focus on today.

First, that EPI is a serious condition affecting infants through adults, and Solvay has substantial clinical experience with Creon.

Our manufacturing process for Creon effectively inactivates enveloped viruses and the realistic risks of non-enveloped viruses are low.

Solvay's clinical proposal for viral risk identification and evaluation will facilitate rapid identification of safety signals, as well as prompt reaction to safety signals should any occur.

[Slide.]

I would now like to introduce Dr. Virginia Stallings, Director of the Nutrition Center and Professor of Pediatrics at Children's Hospital of Philadelphia.

Dr. Stallings will describe the medical need for pancreatic enzyme products.

Dr. Stallings.

Medical Need for Pancreatic Enzyme Replacement Therapy

[Slide.]

DR. STALLINGS: Good morning, everyone. I am delighted to be here and participate on the medical side of this process and I have a few minutes to go over the medical needs for this group of pancreatic enzymes.

[Slide.]

First, just to orient us a little, an anatomy slide, thinking of the food coming down from the stomach, the pancreas, the gland that we have been discussing here, and its primary purpose from a GI point of view is to provide the pancreatic enzymes bicarbonate and some other digestive fluids.

Our goal is to get the food and the enzymes in the upper intestine and the duodenum so that digestion can get started and proceed and we can have effective absorption of the foods and the nutrients.

The real goal of the treatment using pancreatic

enzymes is to normalize that and certainly to support digestion and to prevent malnutrition.

[Slide.]

To take it to the histological level, we are speaking of these cells here. These are the acinar and ductal cells that secrete the pancreatic enzymes, all of the different classes, and really a number of other components of digestion.

[Slide.]

I think it's helpful when you think about pancreatic insufficiency to think about the group of diseases that are inherited and in another group that is acquired. Today, I will be using cystic fibrosis as the major disease in the inherited category. And acquired, we will talk about chronic pancreatitis.

[Slide.]

When you think of the overview, again keeping it broad at this point of pancreatic insufficiency, what happens without the enzymes is you have maldigestion. If the foods aren't digested, they can't be absorbed. And if the foods can't be absorbed, they will be excreted in the stool and resulting malnutrition.

This really has many, many components but I highlight the issues particularly for children of making sure you have adequate fat intake and absorption because of the importance of the calories, the energy for growth, the fat soluble vitamins. But it goes on to include essential fatty acids and a number of minerals.

When you think about this type of a condition, really from the patient's point of view, what you are going to experience abdominal pain, flatulence and steatorrhea, the medical term meaning excess fat passing through and ending up in the stool.

When we think of this in a childhood setting, we really are concerned with growth failure. In children with CF, this growth value goes across the whole gamut, every component. So children won't gain weight. They won't grow tall. Their stature can be delayed and, in fact, even the head circumference can be delayed which is directly related to suppressing normal brain growth.

When we then turn and think about adult patients, you are more likely to think of unintended weight loss as the primary physical sign. In both children and adults, you will see changes in body composition. You will see both

groups of patients losing subcutaneous fat or the energy stores. If the malnutrition goes far enough, you will see changes in the muscle mass, lean body mass and, in both children and adults, we see changes in the acquisition or retention of bone mass, which leads to osteoporosis.

In all the conditions that are affected by pancreatic insufficiency, the malnutrition and the lack of enzymes will contribute to both morbidity and, in many cases, the mortality.

[Slide.]

Now, when talking about this, we have had effective enzymes for about 40 years. But, to point out what late diagnosis of CF and the massive failure to thrive and malnutrition can be, this is a historic slide from the CF Foundation collection showing the terrible malnutrition that you would see if you did not have the kinds of drugs to replace the pancreatic enzymes.

[Slide.]

In a toddler, again with a little bit late diagnosis, you can see the loss of the muscle and the fat stores that would normally be in a child this age, in the buttocks and the legs, and you see the protuberant abdomen,

which is likely a reflection of low protein intake for these kids and ascites.

[Slide.]

Not very long ago I had the opportunity to visit Russia and in talking with some of the patients with the CF there, I met this family. This young man and his mother had really only had access to high quality pancreatic enzymes and antibiotics intermittently.

I was really surprised to find that this young man, who looks like he is about 12 or 13, was really 22, so again an idea of what chronic under nutrition, malnutrition can look like even when it is not fatal.

[Slide.]

As we move forward, we really are talking about replacing these major digestive enzymes, the enzymes in each class, the lipases, proteases and amylases. The medications are given during meals and snacks, basically anytime the patient is taking in food.

The dose is generally determined by the severity of the enzyme deficiency and the size of the meal, the amount of calories and fat in the meal.

Again, the goal is to get the enzymes and the food

in the duodenum at the same time so digestion can take place and we can absorb all of the major nutrients from the food.

[Slide.]

Now, to move just a minute or two on cystic fibrosis and then I will do a minute or two on chronic pancreatitis.

[Slide.]

Many of you appreciate that CF is one of the most common, still fatal genetic diseases in the U.S. There are about 30,000 patients in the U.S. at any given time with CF, and, in fact, that number is growing all the time.

It is important to mention, though, even though we are really talking about the GI side of the disease, that the disease is still dominated by the chronic, unrelenting lung disease, and I will show you some data on morbidity and mortality . I will be using this term FEV_1, which is one of the components of pulmonary function testing and, in CF, has often been the most informative in following the lung disease.

About 90 percent of the people who have cystic fibrosis do have pancreatic insufficiency, thus, would have malabsorption, maldigestion and require enzymes. As I

mentioned briefly with the anatomy slide, it is not just the enzymes but we also lose some of the bicarbonate and fluid secretion from the pancreas and other gut abnormalities also influence the bile acid pool.

Now, two bits of good news. In the U.S., we are on the verge within another month or two of having universal newborn screening, that all children born in all states in the U.S. will be tested by the blood spot that we are accustomed to for many other metabolic diseases.

That leads us into the opportunity that we have never had before, with having earlier and earlier diagnosis, and the opportunity, we hope, to prevent the growth failure that is still common in this disease.

The other thing to mention is that really, certainly over my career, as a pediatrician, most of us learned about death because of the death of teenagers with CF. At that point, maybe a little before 1985 but at that point, the survival rate was 25 years. That means that half of the patients at that point were dying as teenagers or younger and not as young adults.

Today, we are very happy to report that the survival time, the life expectancy is up to 37 years for the

group as a whole, and we expect children born with CF now to have the potential for living into their 50s and 60s just based on the advances we have been making.

[Slide.]

This was the pivotal report, I think, at combining the nutrition and growth part with the pulmonary disease. This was published by Mary Corey in 1988. And what you see in the bright green bar with the shaded area is the survival curve from Toronto, from the Hospital for Sick Children, one of the leading places for CF in the world.

You see the red line or the orange line here was from our leading CF center at the time, which was Boston. The amazing thing that came out of this report was, by the time the patients were 10 years of age, we were beginning to see a statistically different survival rate, that patients being cared for in Canada were surviving much longer than the U.S. and, by the time you do the 50th percent survival, all the way out, people in Canada were living 9 years longer than people in the U.S.

After this paper was really thoroughly vetted and argued about for a while, it really became appreciated that this was due to the difference in how we managed the GI side

of the disease. In Toronto, the idea was give big meals, give plenty of fat, in fact, give a high fat diet and then give enough enzymes to cover the fat.

In the U.S., we had had a tradition where we restricted the fat, because that did alleviate many of the symptoms for the patients. They would have less diarrhea, they would have fewer stomach aches. But as a result we were promoting malnutrition and that, as I said, was a pivotal change.

Now looking at two more modern datasets for CF, this is a report by Konstan, there are two big epidemiological databases in CF in the U.S. This is one that is voluntary and many, almost all, patients are in this. What they did is they looked at the nutritional status of patients when they were 3 years of age and then followed them up when they were 6.

Six is a very important age in cystic fibrosis, because that is when we can begin to collect reliable pulmonary functions tests, again a marker of the lung disease.

What you see here with the children and the A/A category. That means they were well nourished when they

were 3 and they remained well nourished when they were 6 years of age. You can see their pulmonary function reflected by FEV_1 was about 100 percent predicted, really exactly what we want to see.

However, if you were in the next group, the A/B group, that means you were well nourished at 3 but you were less well nourished at 6 years of age. And you can see a clinically and statistically significant drop in the pulmonary function at that point.

The children in the B/B group were poorly nourished at both ages. And you can see again that stair step down and the reduction of lung function. The bit of good news is the patients in the B/A group were poorly nourished at 3. But we did have some improvement in nutritional status by 6 and you can see that the lung function did improve and again was clinically and statistically significant.

[Slide.]

A dataset from Germany again looking across the country showed--and again using 6 year olds is the youngest because of the pulmonary function issue--looking at groups of children divided by school age teenagers and then young

adults--and they divided them primarily using weight and to well nourished and poorly nourished and followed them for three years.

So what you can see in each group; the 6-year-olds, the 12-year-olds, the teens and the older ones, this is where their pulmonary function was if you were well nourished. But in each group, if you belonged to the same age group but were poorly nourished, you had a marked reduction in your lung function and, in fact, here, where we are seeing lung function being relatively stable, we are seeing a slope to this line showing we are losing lung function every year.

[Slide.]

So, out of all of this work recently, the CF Foundation asked for an evidence-based review to look at issues around how should we support patients with CF, both children and adults.

Out of that came the publication in 2008 and it clearly showed from the evidence that if you increase energy intake, you get weight gain. If you get weight gain and height, if you have better nutritional status really by every parameter that we look at traditionally in children,

that will be associated with better pulmonary function and better survival.

Out of this really comes clarity that nutrition management is key to patients with CF who have pancreatic insufficiency, and a high fat diet, or at least a not reduced fat, not restricted fat diet, and pancreatic enzymes are the cornerstones of care.

[Slide.]

Looking at this curve, again to show you we have done better--but there is still a lot of work to do and why I am so excited about newborn screening; this is looking at children across their ages and, looking again just at the weight percentile. These are by birth cohorts.

You can see from the '80s on, we are actually moving kids up on the curve. But what I really want to call your attention to in this slide is the bottom half of a growth chart. What I really need is all of these lines to be up here at the 50th percentile. Again, that is the goal of early diagnosis, early treatment, and I think we can achieve that.

[Slide.]

Just to be specific, now the goal for children is

to have a body mass index of 50th percentile or greater. And that was based on the evidence using the Cystic Fibrosis Comprehensive Patient Registry that showed, when you have children, both boys and girls, with a 50th percentile BMI or greater, it is associated with much better lung function, usually above 85 percent predicted. And below that you see the decline.

[Slide.]

So, now to switch gears a little bit to chronic pancreatitis, which is mostly an adult disease. And it is really, I remind you, from a number of causes you are going to get the same thing, that it's really a chronic inflammatory condition that ends with permanent structural changes of those acinar cells that I showed you. As those cells are killed, fibrotic, they are no longer able to secrete the pancreatic enzymes.

In the U.S., the most common cause for pancreatic insufficiency is chronic pancreatitis, a much bigger group than people with CF. Again, you will find similar symptoms, steatorrhea, weight loss in adults and malnutrition.

When you think of this, it is probably worth again remembering we have people who have primarily a medical

disease, chronic pancreatitis. But we also have people then who have surgical conditions which would be having all of their pancreas removed and then, of course, they have no secretory enzymes or partial. And I will show a little bit of data about both of those conditions and the prevalence of the need for enzymes.

[Slide.]

So, this is a study that was published, that helps really present the idea that if you have chronic pancreatitis and you are put on some enzymes, and you are put on enough enzymes, that the diarrhea and the steatorrhea at least to the patient's view goes away.

That is what happened with this group of patients. Then they were on enzymes for a year. And then they did a second evaluation and what they found then, even though the GI symptoms were gone, there were still a number of signs of malnutrition. I will just mention a couple of them here.

So, at this point, they increased the pancreatic enzymes and really optimized therapy and what they were able to show after that is the patients gained weight in kilos, that the retinal binding protein went up. The retinal binding protein is part of the vitamin A status measurement

and also a good measure of caloric intake and short half-life proteins. And then the pre-albumin again, more short half-life protein in the blood also went up.

So, this was the point of it. It is not just the GI symptoms, but that we really can optimize nutritional status. So we should look for other biomarkers to do that.

[Slide.]

This is the study I wanted to share really looking at the issues of surgery. So patients who have had partial pancreatectomy, they were operated on and then stabilized for about three weeks and then they had a stool fat collection. At that point, the whole group showed stool fat of about 62 percent, which means 38 percent of the fat was being lost in with the bowel movement.

They were then placed on pancreatic enzymes for four weeks to stabilize everybody and then randomized. And, at that point, there was a randomized withdrawal four-week arm. And what you see is the patients now who came up here with 8 weeks of treatment had a significantly improved loss of fat and now they were absorbing 83 percent rather than 62 percent. And the patients who were in the arm that received placebo went from 62 percent down to 63 percent. So, in a

subset certainly of patients with partial pancreatectomy, there is indication for this.

So, in conclusion, I would like to use these two disease conditions really to frame the imperative need for this product. Patients with cystic fibrosis and pancreatic insufficiency, which is about 90 percent of the population, have a life-long requirement for pancreatic enzymes.

This helps them have, for children, grow normally or, hopefully, grow more normally, to optimize their nutritional status, to give them the great immune status to help fight off the lung infections and there is really very good evidence a better nutritional status supports slowing the rate of lung disease.

In people with chronic pancreatitis, you will have a couple of groups. Most of the time adults with chronic pancreatitis develop the need for enzymes over the first decade or so of the disease and then almost everybody, if you go another 10 years, will require enzymes.

If there is surgical intervention, it has a lot to do with what the operation was. If you take out the whole pancreas, they are just like CF, they have a complete need for enzymes. If it's a partial resection, then, there is

the need for the clinician to really sort through which patients now have lost enough pancreatic secretion that they require enzymes.

There are evidence and consensus-based reports for both of these broad classes of diseases, both in the U.S. and in Europe.

[Slide.]

I would like to close to say our goal really is to be able to have products that support not only reasonable digestion and to get the fat out of the stool and decrease the tummy symptoms to really promote optimal growth and development and optimal immune status.

Thank you.

Clinical Efficacy and Safety

DR. SANDS: Thank you, Dr. Stallings.

[Slide.]

Good morning. My name is Earl Sands and I am the Vice President of Research & Development for Solvay Pharmaceuticals. It is my pleasure to share with you the safety and efficacy data for our to be marketed product Creon.

In performing this review, I hope to demonstrate

not only the safety and efficacy of Creon's new formulation in patients with exocrine pancreatic insufficiency but also the similarity between the two products.

[Slide.]

First I will share with you data from our single pivotal trial 3126, which was administered to our to be marketed product to patients with cystic fibrosis. Then, I will share with you the integrated data using our currently marketed product, also administered to patients with cystic fibrosis.

You will see the end results are the same across all formulations. Lastly, I will share our integrated data in patients with chronic pancreatitis or a history of pancreatic surgery and draw some final conclusions. So, let us begin with the 3126 study.

[Slide.]

3126 was a double-blind, placebo-controlled, two-period crossover design. Participants were patients with cystic fibrosis, 12 years or older, who had had a fecal elastase less than 50 micrograms per gram of stool within the last year.

Our target lipase dose was 4,000 units per gram of

fat per day and diets were individualized and contained at least 40 percent of calories from fat. They were identical during both crossover periods.

Now, dosing guidelines were developed in 1995 with formulations that were available at that time and reconfirmation of the appropriateness of these guidelines was supported in publications by Borowitz in 2002 and then again in 2008 by Dr. Stallings. Our dosing scheme was consistent with these guidelines in this study.

[Slide.]

The primary endpoint was the coefficient of fat absorption or the CFA.

Secondary endpoints were a coefficient of nitrogen absorption, clinical symptoms, safety and tolerability.

[Slide.]

The safety sample consisted of 32 patients, 21 male and 11 female. The mean age was 23 with a range of 12 to 43. There were 11 patients who were less than or equal to 18 years of age.

There were 31 patients in the efficacy database, one patient was dropped per protocol after the first crossover period due to a 5 percent weight loss.

[Slide.]

The results for the primary endpoint, the CFA, were highly statistically significant with a treatment value of 88.6 and a placebo value of 49.6.

So, that's important. But we also wanted to know if age had any impact on the final CFA. As you can see, the treatment effect was statistically significant over placebo for both groups, 12 and 18, and the greater than 18 age group.

[Slide.]

We also wanted to know whether the treatment effect was different in individual patients. So here on the x axis are the individual patients and, on the y axis, the coefficient of fat absorption in both the treatment period and the placebo period for each patient.

As you can see, the severity of the disease has no impact on the response to the treatment.

[Slide.]

We also looked at other endpoints. First, the results of the coefficient of nitrogen absorption, one of the secondary endpoints. And you will note that 85.1 percent of the active drug treatment period and 49.9 percent

in the placebo period. This result was statistically significant and, as we had done with the CFA, we looked at the impact of age. And, as you can see, age had no impact, and the result was statistically significant in both age groups.

[Slide.]

Now, we also then looked as another secondary endpoint at clinical symptoms, such as abdominal pain, stool consistency, flatulence and stool frequency. For patients on Creon, 90 percent of the days were pain free and only 58 percent were pain free on patients during the placebo period. Normal stool consistency was obtained in 75 percent of the days on Creon but only 24 percent of the days on placebo.

Now, no flatulence was seen in 42 percent of the days on Creon and 25 percent of the days when on placebo. All measures were statistically significant.

[Slide.]

Here is the data as it relates to stool frequency. The least mean square of stools per day, and you noted that the treated patients had at least one less stool per day.

[Slide.]

So, now let us turn to the safety findings of the 3126 study. Listed here are the treatment emergent adverse events that occurred in more than one patient.

Thirty-two patients were exposed across the two active treatment periods and 31 patients in the placebo treatment period. The third column shows events that occurred in the same patient in both treatment periods.

Note the higher incidence of GI-related events in the placebo treatment period despite a brief treatment period of only 5 days.

[Slide.]

So, in conclusion, Study 3126 demonstrated that the to be marketed product Creon significantly improved the coefficient of fat absorption, the coefficient of nitrogen absorption and symptoms of maldigestion.

The overall incidence of adverse events is higher in the placebo period and is driven by GI-related disorders.

[Slide.]

So, now let's look at the integrated data from our currently marketed product in patients with cystic fibrosis.

Here are the three controlled trials across a broad range of ages. On the first line is the 3126 data for

comparison. And you will note that despite age or baseline CFA, the end CFA results are greater than 80 percent.

[Slide.]

Now that we have looked at the data for the to be marketed product, let's turn to the results for the trials of the currently marketed product again. Our purpose here is to demonstrate the similarity between the two products. So on the x axis is the CFA at baseline and on the y axis shows the change from placebo to active treatment.

First, let's look at the 3126 in the to be marketed product. Now let me show you the same age group in the currently marketed product.

Finally, let's look at the results using the currently marketed product in age groups 7 to 11 and then in the infants ages 1 month to 24 months. As you can see, regardless of age, formulation, or study design, patients with the same baseline CFA experienced the same improvements in CFA.

[Slide.]

Now, let's look at the adverse event profile for both the adverse events and the treatment emergent severe adverse events in the currently marketed product.

First, we see a very low withdrawal rate due to any adverse events and, secondly, we see a higher rate of treatment adverse events in the zero to 4 age group and the greater than 30 age groups. These numbers are driven by GI and respiratory disorders in the zero to 4 group and infections and infestations in the greater than 30 age group, and we will provide you a little more detail on the next slide.

[Slide.]

While this is somewhat of a busy slide, it is important to note that many of the adverse events from the integrated analysis, such as GI and respiratory disorders are consistent with the disease complications as seen in patients with cystic fibrosis.

In the case of infections and infestations in the zero to 4 age group, as one would expect, they are consistent with the medical literature. The majority of events are respiratory infections commonly seen in children of this age.

[Slide.]

So, in conclusion, in patients with cystic fibrosis, the efficacy and safety results for Creon are

consistent across formulations and across age groups.

Creon's to be marketed formulation is clinically comparable to the currently marketed product. Therefore, we conclude that Creon is safe and effective for its indicated use.

[Slide.]

Now, let's look at the data from the currently marketed product in patients with chronic pancreatitis or a history of pancreatic surgery. In the two trials with patients with chronic pancreatitis, the resultant CFA was greater than 80 percent irrespective of the baseline CFA.

In our trials in patients with a history of pancreatic surgery, the resultant CFA was also greater than 80 percent.

[Slide.]

Now, let us look at the treatment adverse events in these same trials. You will note that there is a small difference from placebo to placebo in the treatment emergent adverse events, and there is a similar incidence of treatment emergent adverse events between treated groups and placebo.

In the next slide, I will share with you the

specific adverse events for patients with chronic pancreatitis.

[Slide.]

In our trial, there were a slightly higher number of treatment adverse events of abdominal distention and constipation versus placebo.

[Slide.]

Now, let's look at the patients with the history of pancreatic surgery. The results are similar except for the treatment adverse events of diarrhea and hyperglycemia and, as you will note, the glucose control is challenging in patients with a history of pancreatic surgery due to the primary disease.

Since Creon has an amylase component, it is not surprising that we might see evidence of increased glucose absorption. We would recommend that patients be monitored closely in the initial stages of treatment for fluctuations in glucose levels.

[Slide.]

These studies demonstrate that the to be marketed Creon, like the currently marketed product, is both safe and effective in treating patients with symptoms of maldigestion

due to chronic pancreatitis or a history of pancreatic surgery.

The most frequent treatment adverse events were GI related and consistent with the underlying disease.

[Slide.]

So, in conclusion, Creon improves maldigestion in patients with exocrine pancreatic insufficiency as seen by statistically significant improvements in CFA and the nitrogen absorption CNA.

Creon also improves clinical symptoms of abdominal pain, stool consistency, flatulence and stool frequency. All of these benefits are seen regardless of age.

Creon has demonstrated a favorable safety profile in patients with exocrine pancreatic insufficiency across all age groups and regardless of etiology.

Adverse events were less than or similar to placebo and most adverse events were related to the underlying disease process.

[Slide.]

As the manufacture of Creon involves the elimination of viruses that pose a small but theoretical risk to humans, I would now like to introduce Dr. X.J. Meng

from Virginia Tech, who will discuss the viruses, the potential for human infection, and the way in which they are eliminated through both physical and chemical means.

Dr. Meng.

DR. McGOWAN: Thanks very much.

Can I just let the Solvay pharmaceuticals team know they have 20 minutes remaining of their allotted time, just to give you a heads-up. Thanks.

Dr. Meng.

Assessment of Porcine Viruses

DR. MENG: Thank you. Good morning everyone.

[Slide.]

I am X.J. Meng, and I am a virologist from the Virginia/Maryland Regional College of Veterinary Medicine at Virginia Tech.

[Slide.]

So far you have heard about the evidence for medical need for this product and you also heard about the clinical safety and efficacy of this product.

Since this product is derived from pig tissues, I am going to spend the next five minutes or so to talk about the potential risk of viruses in this class of drug, the

porcine drug products.

[Slide.]

Many viruses are known to infect pigs and, in fact, more than 30 of them are known to infect pigs. These large number of viruses pose a tremendous challenge for the detection and control of these viruses by the veterinary community and these viruses also pose a potential risk of human infection.

However, in the next five minutes or so, I am going to try to show that based on existing knowledge in the published literature, the risk of infection through the use of this product is very small.

[Slide.]

Now, in general, the viruses can be classified as enveloped viruses and non-enveloped viruses. Shown here in this slide, it's the typical enveloped viruses. You can see the nucleocapsid, the protein of the virus. And it is surrounded by the viral envelope. On the viral envelope, you can see the viral proteins and also the lipid molecules.

The lipid molecules are very abundant and account for somewhere between 20 to 35 percent of the dry weight of the envelope viruses. So, because the lipid-rich envelope,

this group of viruses are very sensitive to inactivation by a variety of forces including the temperatures and lipid solvent.

So, consequently, the enveloped viruses survive a very short period of time in the environment and they are relatively easier to get rid of and, generally, they cause seasonal diseases. Disease occurs usually in cold regions that favor the survival of the virus.

[Slide.]

Shown here in this slide are some of those enveloped viruses that are known to infect the pig that has either the confirmed zoonotic risk or has the potential to cause zoonotic infections.

The narrow definition of zoonotic infection is the transmission of viruses from vertebrate animals to humans. And you can see here a list, about 8 or 9 of those viruses that either confirm zoonotic or has the potential to be zoonotic.

I don't have the time to go through all these viruses, but I want to just quickly point out here that some of the viruses, even without any negative issues, they do not really pose a real concern.

For example, the West Nile virus, the Eastern Equine encephalitis virus, those viruses are transmitted by the mosquito, through the bite of the mosquito, and the Rabies virus. And there are only about 30 cases of Rabies in the last 10 years in the United States and they are transmitted by the bite of rabid animals.

So, as the common knowledge, the enveloped viruses are sensitive to inactivation by heat and also by lipid solvent. Shown here on the right column of these slides are some of the published data showing effective inactivation by heat. Essentially, all the enveloped virus can be effectively inactivated by heat at 56 to 60 degree within one hour.

[Slide.]

Now, for non-enveloped viruses, the nucleocapsid is the completed virion and they are more resistant to inactivation. Consequently, they can survive in the environment for a longer period of time and they cause non-seasonal, year-round disease.

[Slide.]

Shown here in this slide are the non-enveloped virus. There are about five or six of them here with a

confirmed zoonotic risk or has the potential risk for zoonotic infections. Unlike the enveloped virus, however, this non-enveloped virus, they have variable sensitivity to inactivation.

In most cases, you can see here from the data published out here--in most of these viruses, they can be effectively inactivated by heat at 50 to 67 degrees. However, their sensitivity to lipid solvent is not great. They only can be inactivated 2 to 4 logs.

[Slide.]

Very briefly, I am going to talk about some of the non-enveloped viruses in terms of their zoonotic potential. One of the viruses is the swine hepatitis E virus. This virus is widespread in pigs. And this virus is the confirmed zoonotic virus and the swine hepatitis E virus can infect human.

[Slide.]

One thing I want to mention here is that only genotypes 3 and 4 HEV so far has been isolated from pigs, and these two genotypes are associated with only sporadic cases of hepatitis E. And the genotype 1 and genotype 2, those cause epidemics and outbreaks, and they are

exclusively restricted in humans.

[Slide.]

The swine vesicular disease virus, this virus is potentially zoonotic. There are some early reported cases of human infection although severe disease has not been reported recently, not even the lab personnel who handle large quantities of the viruses.

So, it is possible some of the early reported cases may be actually caused by some other viruses.

[Slide.]

The encephalomyocarditis virus, EMCV; this virus is a potential zoonotic virus. However, so far there has been no definitive association between EMCV infection and human disease even though the antibody to this virus has been reportedly detected in selected populations of humans such as hunters.

[Slide.]

The last two viruses in this category are reovirus and rotavirus. These two viruses are potential zoonotic. It has been shown that human rotavirus recovered from diarrhea patients contains genes that are characteristic of porcine rotavirus and, therefore, suggestive of potential

cross-species infections.

[Slide.]

Besides these non-enveloped zoonotic viruses, there are two other viruses, also somewhat of concern, and they are the porcine parvovirus and the porcine circovirus.

Now, these two viruses are not zoonotic, and the reason why they are of concern is because they are very resistant to inactivations.

For the porcine parvovirus so far there is no evidence of human infection and, in fact, in one of the porcine drug products, the hep C factor VIII products, it has been shown that this product was contaminated by the porcine parvovirus. However, patients who received this contaminated product have no evidence of the infections.

Now, Dr. Colin Parrish's group from Cornell has done a lot of studies showing potential cross-species infection. In fact, in the feline parvovirus commuted its genome and, in fact, does, and this mutation caused the host switch.

Now, could such an event also occur for the porcine parvovirus. And the answer is we really do not know. It is very challenging to monitor the evolution of

viruses in the pig population or even in individual hosts, largely because these viruses do not cause disease all the time.

[Slide.]

The last virus I want to mention is the porcine circovirus. Again, there is no evidence of human infection for this virus. There was a single report of detection of porcine circovirus antibody in humans about 10 years ago from a German group. However, in a subsequent study done could not verify those results.

So, it is possible that the early report of detection of circovirus antibody in humans could be due to cross-reaction with other entities.

The genome of circovirus so far is relatively stable and there were no changes after three consecutive passages in pigs. There are only three changes after 120 passages in the porcine cells.

[Slide.]

So, in summary, the enveloped viruses are sensitive to the inactivation by heat and by lipid solvent, and they can expect to be inactivated by those treatments.

The non-enveloped viruses, however, are variable

and it is likely that we can detect the viral nuclear acid, the remnant in the viral genome, not necessarily affects the virus in those porcine drug products.

It is also possible that for those highly resistant viruses, such as porcine parvovirus and porcine circovirus, even the infection virus may be detectible in those porcine drug products.

However, the chance of causing human infection in patient who received this product is very unlikely, largely because of the nature of this virus. They have not been shown to infect humans and they are generally considered to be species specific.

So, consequently, the transmission of the virus to those where you are in close contact with the patient and causes epidemic and spreading the virus to the general public is very unlikely.

In theory, yes, there is a potential risk to the patient who received the products. But, in reality, the risk is very small.

In conclusion, as an early administered drug, I would like to say that the chance of infection by the drug is no more than the product that we eat as food from the

grocery store.

With that, I am going to conclude my talk and thank you.

Risk and Mitigation Strategies

DR. SANDS: Thank you, Dr. Meng.

[Slide.]

While Solvay believes that the potential for viral infection is, as Dr. Meng has said, very small, we nevertheless acknowledge the benefit of a proactive surveillance program that monitors any activity that may suggest the presence of a viral infection in the patient population.

For the next few minutes, I will review Solvay's draft program which has yet to be formally submitted to the agency and we value your comments and look forward to discussing the plan with you more in detail.

[Slide.]

I will begin with a review of the background of the theoretical risk to humans and then present our proposed program which uses retrospective information to establish appropriate assumptions and benchmarks to use in developing a proactive, prospective program to identify and monitor

potential changes in viral activity.

I will also touch on labeling considerations.

[Slide.]

Let me remind the panel of our discussions this morning that all porcine-derived products have an inherent risk associated with virus. While we know that there is a risk of porcine viral contamination, let us be clear that the presence of virus does not translate into human infection unless the virus is zoonotic or a non-zoonotic virus mutates into a zoonotic virus.

It is important to note that Creon has been marketed for over 20 years, comprising more than 5 million patient years of experience and, in our entire clinical and postmarketing database, we have been unable to identify any pattern of viral illness.

[Slide.]

As discussed this morning, Solvay's manufacturing process minimizes the potential viral load through three key pillars of viral safety starting with the control of sourcing of the swine pancreases.

The second step is inactivation during the manufacturing process, which essentially inactivates any

risk from enveloped viruses and, as Dr. Meng said, non-enveloped viruses are more resistant to inactivation by chemicals or heat and several do remain.

Our third pillar is to test for the potential remaining viruses to ensure that they meet specifications and to reject and to destroy any material that does not meet these specifications.

[Slide.]

To paraphrase Dr. Meng, there is a remaining theoretical risk although the potential for human infection is very, very small and requires zoonosis or emergence of a de novo zoonotic virus.

[Slide.]

The proposed program includes both a retrospective and prospective element. Let's turn to the retrospective studies first.

[Slide.]

The retrospective studies allow more in-depth review of available information to understand the potential prevalence of viral infections in two different and complementary databases and, if feasible, allow us to conduct a formal epidemiological study to compare the

potential incidence of viral disease between PERT users and controls.

[Slide.]

So, first, let's talk about the MarketScan database. This is a large U.S. claims database covering 33 million patients for up to 12 years, that documents in-and-out patient encounters and enabling the linking of prescriptions, diagnoses and medical events.

Our analysis will begin with a feasibility assessment whether the database will enable the calculation of an incidence and prevalence of infectious diseases with attention to GI infections associated with PERT use exposure.

Assuming the analysis provides usable information, then, further data cuts could be taken going forward. This data can be used to help plan and size the prospective active surveillance program that we will be discussing in just a few moments.

[Slide.]

The second is a retrospective database study utilizing the UK general practice research database or the GPRD. This database covers 6 million lives and 60 million

patient years. It provides a high quality information on drug exposure and medical events and offers the opportunity to request further information on a specific patient or an event.

Based on our initial query, there appear to be over 5,000 ever users of pancrelipase. Our analysis will include calculation of predefined diagnoses and conditions of interest, comparing pancrelipase and control populations.

[Slide.]

Now, let's move from the retrospective to the prospective components of our program.

[Slide.]

First, briefly, the veterinary surveillance. As describe in far more detail this morning by Dr. Rueffer, Solvay will remain vigilant in its understanding of viruses in the veterinary world.

The process includes regular scientific literature searches, networking with virology, swine disease and zoonotic experts, doing trend analysis in the food industry and also regular sequence alignments and testing of unknown viruses in an SK6 cell line for every batch.

[Slide.]

Our first prospective clinical activity involves collection of data using the Cystic Fibrosis Foundation registry. We will augment the case report forms that are routinely completed at regular intervals by all patients to gather additional information about conditions of special interest.

These signs and symptoms will be defined by stakeholders and these stakeholders would include the FDA, the Cystic Fibrosis Foundation and treating health care providers. And we look forward to an iterative process to develop this program in partnership with the Cystic Fibrosis Foundation which has already provided their agreement to this program in principle.

In addition, we propose to establish sentinel sites within the CF treating population. These sites will work within the environment of a pre-approved protocol developed with the input of the previous listed stakeholders, and these clinics will collect on a routine basis blood and stool samples.

They will be asked to respond to changes in patient condition with similar collections. These samples will be analyzed using available state-of-the-art technology

to detect viral presence, and we are open to considering whether serum samples could be stored for potential testing at a future date with yet to be invented technology.

[Slide.]

Presently, the availability of bioassays for viral detection and identification is limited across species and so, until there is further comprehensive bioassay development monitoring, will continue to remain a challenge.

[Slide.]

We believe that our program is comprehensive and robust and it is appropriate given the limitations of the available data, which include difficulty in differentiating the natural history of the disease in viral infections, and it is confounded by multiple alternative potential sources of contamination such as food and the lack of presently validated commercially available viral assays.

Our strengths temper these concerns by utilizing multiple sources of data and taking a proactive approach and conducting these studies in a highly reliable compliant and representative population.

[Slide.]

The FDA has asked for input on appropriate

labeling related to viral risk and we agree that including this information in the label is appropriate as the best way to balance informing both the practitioner and the patient without having an adverse effect on usage and compliance with the dosing regimen.

We would recommend class labeling that includes the key points about the manufacturing process, the parameters associated with residual risk, and the importance of the health care professional communication and education of patients.

Now, let me briefly conclude our presentation of this morning.

Conclusions

DR. RACZKOWSKI: Thank you.

[Slide.]

The need for pancreatic enzyme replacement is indisputable. Creon and products like it are essential to the treatment of cystic fibrosis, chronic pancreatitis and patients with a pancreatectomy in achieving positive outcomes.

These products are essential for many of these patients to achieve adequate nutrition. They extend lives

for many and substantially improve the quality of lives for others. Said simply, for many of our patients these products are essential for life itself.

The clinical benefit of Creon in use is clear and the risks in the form of adverse events are generally mild and difficult to separate from the underlying disease.

Creon is clearly efficacious as shown by the improvements of both CFA and the symptoms associated with pancreatic exocrine insufficiency. Of critical importance, these benefits are seen regardless of the underlying etiology of the age of the patient.

[Slide.]

Turning to the other areas of discussion as we had this morning, the Creon manufacturing process is robust and controlled by Solvay from the initial sourcing of the pancreatic glands through a vigorous and highly effective manufacturing process and on to the final testing and release of the product for distribution.

The integrated viral quality system utilizes state-of-the-art technologies to reduce the residual viruses in Creon to minimal levels while maintaining the effectiveness of the enzyme active ingredients.

As you have heard from Dr. Meng, the microscopic levels of viruses that remain in Creon pose a very small, perhaps one could even say minute risk of creating human infection at the current time.

But what about the future, what is the potential for a viral outbreak in the current product or the potential of a new mutant strain of a virus to appear?

As you have heard from us and from external experts, we believe the risk is very, very low and we have taken appropriate steps to keep it at the minimal level by implementing an active surveillance program that monitors all steps along the sourcing and manufacturing chain and in the population at large. Solvay is proud of its long history and the impact we have been able to have on the lives of millions of patients.

We stand behind our product and believe that our development program in the terms of clinical evaluation, manufacturing and proposed in-market surveillance activities merits your support for the proposed indication, which is treatment of patients with maldigestion due to exocrine pancreatic insufficiency.

[Slide.]

This concludes our presentation and together with the experts listed on this slide, we would be pleased to answer any questions you may have.

Thank you.

DR. McGOWAN: Thanks very much.

We would now like to proceed to the FDA presentations and I think our first speaker is Dr. Ethan Hausman.

Presentations from FDA

NDA 20-725 Pancrelipase Delayed Release Capsules (Creon)

DR. HAUSMAN: Good morning.

[Slide.]

Good morning. I would like to welcome everybody to today's meeting of the Antiviral Drugs Advisory Committee. We are discussing New Drug Application NDA 20-725 Pancrelipase Delayed Release Capsules (Creon). I am Ethan Hausman. I was the clinical review officer for this project.

[Slide.]

The clinical background has already been discussed. Creon is a porcine or pig derived pancreatic

enzyme replacement product, or PEP, and is used to treat pancreatic exocrine insufficiency, or PEI. Creon contains lipase, amylase and protease and, due to deficiencies of these endogenous enzymes, there is fat, protein, carbohydrate malabsorption with gastrointestinal symptoms such as flatus, bloating, voluminous fat laden stools and, in children there is stunted growth.

Below on this slide we see two conditions that are characterized by pancreatic exocrine insufficiency, or cystic fibrosis, and chronic pancreatitis and treatment effect for these patients is assessed by a change in clinical symptoms, improvement in clinical symptoms, decreased bloating, flatus and improvement of a marker called coefficient of fat absorption, which we have discussed earlier in other presentations and I will explore later in the talk.

At the bottom of the slide, we can see that improvements in coefficient of fat absorption have been shown to lead to improved nutrition, improved growth and pulmonary function and, ultimately, to improved long-term outcomes.

[Slide.]

This slide is taken from a recent Cystic Fibrosis Foundation annual report. We can see that since the early 1960s, the median survival of patients with cystic fibrosis has increased from approximately 1 year to about 37 years as of 2006.

Now, as discussed earlier in today's talks, not all of this improvement in survival is due to treatment with PEPs. However, it is an important component to the benefit that these patients have seen over the years.

[Slide.]

A little bit about the regulatory history of PEPs. They have been available in the United States since prior to the Food, Drug and Cosmetic Act of 1938 and currently available PEPs are marketed as nutritional supplements rather than as new drugs.

On the left-hand part of this slide, we see that drugs are marketed under laws that require demonstration of safety and efficacy for the labeled indication, consistent purity and potency of the drug, consistent adherence to good manufacturing practices and accurate labeling.

Nutritional supplements, on the right-hand part of this slide, we see are generally regulated as foods. The

law does not generally require FDA review or approval prior to marketing. However, manufacturers are responsible for determining safety of their products and for determining accuracy and truthfulness in their labeling.

[Slide.]

In the 1990s, FDA evaluated the safety and effectiveness of the then available PEP products in an effort to determine the appropriateness of allowing these PEPs to be marketed as non-prescription or over-the-counter drugs.

In 1995, based on a large body of clinical evidence including data received from the public, FDA determined that there was sufficient clinical evidence to support improved clinical outcomes for patients with pancreatic exocrine insufficiency treated with PEPs, such as patients with cystic fibrosis.

[Slide.]

However, several issues with then available products were determined to be potentially affecting safety and efficacy of these products including potential transmission of porcine viruses, which is the main topic of today's advisory committee.

Additionally, there was variation in bioavailability among similar dose forms, between different manufacturers and, for members of the audience and the Advisory Committee, this is a situation where two manufacturers make a very similar product which is supposed to have the same labeled strength. But product A and product B on higher level testing actually wouldn't have, in that scenario, similar activity.

Below this we see variability in variation in bioavailability within the same product. So that means one manufacturer's product, two different bottles of the same product, might not have the same activity.

Additionally, at that time, FDA recognized that patients with diseases requiring PEP therapy needed medical monitoring and this necessitated a prescription-only status rather than over-the-counter status.

Therefore, FDA determined that PEPs did not meet the regulatory definition of safe and effective drugs. And FDA determined that New Drug Applications, or NDAs, would be required to bring PEPs to market through adequate drug development processes.

As has been noted earlier today, FDA published a

Guidance for industry regarding requirements for new drug applications for PEPs. In addition to addressing manufacturing issues such as the lot-to-lot variability and the viral issues, the Guidance specifically addressed clinical study requirements.

[Slide.]

Because of the wealth of clinical data that existed to support improved clinical outcomes with PEP treatment, it was established that the safety and effectiveness of PEPs could be demonstrated by a single short-term adequate and well-controlled trial in a well-characterized diseased population, such as a two-week crossover study in 10 to 25 patients with cystic fibrosis.

At that time it was also determined that there was adequate clinical evidence to establish stool fat markers, such as coefficient of fat absorption for determining efficacy.

[Slide.]

Also, since children with cystic fibrosis would be a recognized need group, evidence of safety and efficacy in pediatric subgroups was required, and evidence from one group can be used to support extrapolation to other groups.

Additionally, demonstration of efficacy was required to be shown at doses of 2,500 Lu/kilo/meal or less, or 4,000 Lu/gram of dietary fat/day or less.

Why were these levels, these cutoff levels chosen?

Well, the Cystic Fibrosis Foundation, in concert with FDA, recognized that there were increasing reports of a very serious adverse reaction called fibrosing colonopathy, which can eventually lead to colonic stricture, and risk was found to be associated with increasing lipase dose and increasing duration of exposure; so higher dose, longer duration, higher risk.

These levels were determined to be at a level that was below where this cut point for increased risk was recognized. Additionally, increases of coefficient of fat absorption with lower doses have been established.

Additionally, the Guidance noted that assessments for viral risk and demonstration of removal and/or inactivaton of viral agents needed to be demonstrated per International Conference on Harmonization document Q5A.

[Slide.]

Which brings us to the regulatory history of Creon. In 1997 NDA 20-725 was submitted. In October of

2003, the agency determined that additional information would be required. In 2006, Solvay submitted additional information and, in August of 2007, the agency determined that additional clinical information would be required including one or more studies with the product that was intended to be marketed at the time of approval, which brings us to the study we will discuss today, the pivotal study which was received by the agency in June of 2008.

[Slide.]

This is the only study that is used for determination of safety and efficacy. This is the first completed randomized, double-blind placebo-controlled study with the intended to be marketed product, which I will refer to as Creon for the rest of the talk and, just to highlight for the Advisory Committee no prior adequate and well-controlled studies have been performed to date with the intended-to-be-marketed product.

[Slide.]

The study design has already been discussed. This was a multi-center, 3-week, randomized, double-blind, placebo-controlled, cross-over study in 32 patients with cystic fibrosis from 12 to 43 years old.

There were two treatment groups. The first group got Creon followed by placebo, the second group got placebo followed by Creon.

As we can see, patients served as their own controls, which is, in this particular case with this disease model, appropriate.

[Slide.]

Inclusion and exclusion criteria were already discussed. One thing that had not been mentioned earlier is that all patients for enrollment had to be on treatment with some other non-Creon PEP at a stable dose at the time of enrollment.

Exclusion criteria included a history of fibrosing colonopathy or a weight loss greater than 5 percent within 3 month prior to the study.

[Slide.]

Dose, again, was 4,000 Lu/g dietary fat/day. Again, this was designed to be consistent with cystic fibrosis and FDA guidelines. Again, this is at the upper limit.

[Slide.]

Here, we see the study schedule. On the left-hand

part of the slide we see that the screening procedures were completed. Patients stayed on their prior PEP therapy until they entered the first cross-over period where they received treatment for 5 to 7 days, still fat assessments began on the evening of Day 2 and beginning of Day 3.

This was followed by a washout period, which is not a conventional washout period for the hardcore scientists in the audience.

During this period, patients resumed their prior PEP rather than no treatment at all. This was followed by the cross-over period 2 where patients received the opposite treatment that they had received during the initial cross-over period.

This was followed by a safety period of approximately 1 week where additional safety information was collected from adverse events that occurred in that time period.

[Slide.]

Demographics have been discussed. The median age and mean age was approximately 22 years and was very similar in the two treatment groups. Slightly more males enrolled than females. Cystic fibrosis is not a solo disease. But

the literature doesn't support differences in severity by gender, so this was not felt to be clinically meaningful for assessments of efficacy.

The most important part of the slide is on the bottom where we see placebo CFA. We didn't have pre-existing non-treatment CFA on a lot of these patients, so we used this as sort of a proxy for what somebody's baseline CFA was, and 40 percent was chosen because literature suggests that 40 percent CFA or less is a marker of more severe disease whereas non-treatment CFAs of above 40 percent is relatively milder disease. These are arguable cut points, but this is what we chose.

[Slide.]

There were two efficacy populations. The full analysis population, these patients were treated with Creon and placebo, and had CFA from both cross-over periods.

The modified full analysis population excluded data from two patients where diet and dose could not be performed. I will be discussing the efficacy results from the MOD-5 analysis population only.

[Slide.]

Here we see that the efficacy assessment was the

mean difference in CFA from Creon treatment minus placebo treatment, and this equation of CFA up here shows us that it is actually a ratio of how much fat one absorbs compared to the load delivered to the mouth.

[Slide.]

In this table of the change in CFA, we can see here on the right-hand part of the slide the mean difference, the adjusted mean treatment difference, in CFA from Creon minus placebo was 41 percent, and the p-value was less than 0.001. So these results are clinically meaningful and statistically significant.

Perhaps as meaningful, we see that the 95 percent confidence intervals, the lower 95th percent confidence interval, is 34 percent so even the least responsive patients appeared to have a change in CFA above 30 percent, which is again supported in the literature as defining a clinically meaningful response.

[Slide.]

Sensitivity analyses showed no clinical meaningful differences in response by age or gender and, again, effects by race could not be assessed even though this was a multi-center and potentially multi-national study. All the

enrolling centers were in the United States, and this was consistent with the demographics of CF in the U.S. population.

One sensitivity analysis of note, when we stratified by placebo period CFA of less than 40 percent and less, we found that patients with lower CFAs had a mean increase of 60 percent CFA, and patients with CFA over 40 percent had a mean increase of 30 percent.

[Slide.]

Safety. Briefly, patients were treated with 5 days of Creon therapy. There were no clinically meaningful differences in dose by demographics.

[Slide.]

There were no deaths. One patient withdrew due to a violation of enrollment criteria. Two serious adverse events were reported in 1 patient who was in the placebo to Creon arm. This patient had duodenitis and gastritis over 2 weeks after the last Creon dose.

As I said earlier, the safety follow-up period was 1 week later but, apparently the data lock was sometime after that. So this patient's duodenitis and gastritis happened after they had transitioned back to another PEP

therapy and it is very difficult to establish a relationship of these two events to Creon.

[Slide.]

Here, we see a table of common adverse events. Actually, we will go to the meat of the matter at the bottom. The patients with any adverse reactions;more patients during placebo treatment had adverse reactions than during Creon treatment, and that's 50 percent of patients during Creon and 71 percent of patients during placebo.

We can see as we move to the top of this slide that this difference was very much driven by difference in gastrointestinal adverse events, such as abdominal pain and flatulence. It was more common in placebo treatment than Creon treatment.

This is an intersection, if you will, of how safety and efficacy in this particular product overlap. You wouldn't see this in other kinds of drug products or you might not see this in other kinds of drug products.

[Slide.]

There were no cases of fibrosing colonopathy reported in this study. However, I would like to point out to the Advisory Committee and the audience fibrosing

colonopathy is a histopathologic condition. Surveillance procedures, such as colonoscopy and biopsy, were not incorporated into the pivotal study. However, because of the short duration of the study and doses which were below level that is recognized to cause or be associated with fibrosing colonopathy, no cases were expected.

[Slide.]

Clinical laboratory studies were generally unremarkable. Of note, specific assessment of blood uric acid levels was done because reports in the literature of treatment with PEPs being associated with hyperuricemia and hyperuricosuria, and there are no differences in blood uric acid levels from Creon to placebo treatment.

Notably, 3 patients had decreased neutrophil counts with Creon treatment. Only one patient reached a clinically recognized definition of absolute neutropenia with a level below 1,500 cells per microliter.

There is no notable concomitant adverse events in these patients and there is no association of PEP treatment with neutropenia in the literature.

[Slide.]

In summary, the efficacy of Creon capsules has

been demonstrated in patients with cystic fibrosis, 12 years and older. The adjusted mean difference in CFA from Creon minus placebo was 41 percent with a p-value of less than 0.001, and the short-term safety of Creon capsules has been demonstrated in patients with CF, 12 years and older.

[Slide.]

Here are my references. I would like to thank everybody for attending the conference today and take this opportunity to introduce my colleague, Dr. Barry Cherney from the Division of Therapeutic Proteins, who will be discussing the viral issues.

Thank you.

Viral Safety Issues for Pancreatic Enzyme Product Creon

DR. CHERNEY: Good morning.

[Slide.]

My name is Barry Cherney. I am the Deputy Director of the Division of Therapeutic Proteins. Part of our responsibilities with the FDA is that we evaluate drug products quality as it relates to safety and efficacy. So what I was going to do today is to talk about the viral safety issues for the pancreatic enzyme product Creon.

[Slide.]

By way of overview, I would like to give a little brief background on the PEP Guidance document and talk specifically about some product quality considerations. And then I will go on to a general introduction to the viral issues and followed by a viral risk assessment with a focus on porcine parvovirus and porcine circovirus that you have heard from Solvay today, and examples of FDA's management for parvovirus risks and risks associated with xenotransplantation and, finally, a short section on the risk mitigation strategies.

[Slide.]

To start with, in April 2006, FDA published Guidance for Industry on Exocrine Pancreatic Insufficiency Drug Products. These considerations had clinical, non-clinical, as well as administration issues and information on how to submit NDAs.

It also recommended improved assurance of drug product quality and consistency.

There are several key considerations that I think we should mention. One is the control of manufacturing, which was not explicitly mentioned in the document but is a

requirement for all NDAs. This means that there is stricter adherence to good manufacturing practices, establishment of in-process controls such as well defined process times.

These all are requirements and the essence to ensure that there is manufacturing consistency and hopefully, with that, increased consistency of product quality.

Another issue that was mentioned in our Guidance document was the physicochemical and biological characterization of the drug substance. This was with the idea that if you identify critical product attributes and migrate them on to release testing, that then you can have a better assurance of product quality and product consistency.

In addition, the existing release testing that was already being performed should undergo formal validation, and that is to make sure that the release assays--in particular--the potency assay was reproducible, was sensitive, and was accurate.

Finally, improvements in stability profile was of particular concern given that overages had previously been associated with adverse events.

So, in this case, then, overages to compensate for

loss during storage are not permitted. In fact, the potency of lipase strictly must reflect the label claim.

[Slide.]

A general introduction to the viral issues.

[Slide.]

When FDA ruled that PEPs should be available by prescription only, the viral issues were not explicitly identified as a product safety or quality issue although we certainly recognized that those issues were there.

Historically, most PEP manufacturers have neither monitored viruses nor evaluated the manufacturing process for viral inactivation, presumably because of the lack of perceived risks. After all, this is oral administration of a food grade product and there is presumed safety with that.

The process does have some potential to inactivate viruses and that was I think well known. But, most importantly, there was a long history of safety regarding viral infections. There is no documentation of transmission of an infectious disease despite very extensive use and through multiple manufacturers.

However, risk of transmitting a disease from animal-based drugs, although it appears low, is valid

concern. Swine populations are infected with known and perhaps unidentified viruses.

[Slide.]

So, some of the general risk consideration is that pork that you eat is usually cooked at 170 degrees or cured, and that reduces the viral load by some measure. Of course, it is difficult sometimes to cook these products, so one of the questions is how much heat inactivation should be applied.

The results of issue that viral load and muscle versus pancreatic tissue is very different and, in fact, we really don't know what those loads are. Furthermore, Creon is designed to be released in the small intestines, which bypasses low ph environment of the stomach. This actually inactivates some, but not all, viruses. But, in FDA guidance, this is viewed as a very robust viral activation method.

Another risk consideration is the intensity of exposure. This is a chronic use of product with potentially chronic viral exposure. For example, a patient of body weight of 60 kg could receive up to 3.75 grams of pancrelipase daily. So there is a huge amount of product

being taken.

Now, in the past, there was no requirement for reporting adverse events pertaining to the PEPs to the FDA. We had some oversight but not the typical oversight that you see and we do not have all these adverse event reports to go back and look at data.

Additionally, adverse event reports themselves are a blunt instrument. For example, some patient populations using PEPs have high background rates of infections so it may be difficult to discern infectious disease events related to the use of the product specifically.

[Slide.]

Some of these concerns actually were highlighted in the New York Times article dated April 1, 2008, "Seeking Alternatives to Animal Derived Products."

I would like to go through a couple of the points and quotes that were actually made in that article. One was that a pet 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."

I think this clearly is indicating that yes, live

viruses could be present in the drugs but that, in order to eliminate those, we are going to have problems making the drug available.

I think the term, though, "not dangerous" is a relative term because, as mentioned previously, there is no zero risk, there is some level of danger and part of the purpose here today is to decide what that level of danger is. We recognize it is a low danger, but there is some risk.

The article also raised the possibility that unidentified viruses or other contaminants could threaten the supplies of the drug and I think, with the risk of emerging viruses, there is always that potential risk.

I think it is striking to see that when you look at the types of viruses that were present in swine populations 20 years ago, and look at them that are present today, you see that there are striking differences. Viruses have emerged, so this is an evolving issue.

But I think the other thing that was not addressed is what are the risk mitigation strategies that Solvay can employ that could actually mitigate the risk that the drug supplies are threatened.

Finally, it is also quoted that the FDA said that viruses must nevertheless be eliminated or rendered inactive. We believe this statement was actually taken out of context, because of all you have heard, we are not going to be able to eliminate the viruses of the product. Because of the source of the tissue and the manufacturing process itself, we are not going to completely eliminate all viruses or inactivate them.

I think we can reduce the frequency. You can reduce the viral load, but total elimination is not possible. But I think it does highlight--besides the concerns for these products, it also highlights and reinforces FDA's belief that our regulatory decisions regarding these products should be transparent, based on good grounded science and risk-based approaches and seek the advice of independent external experts. And that, in large part, is why we are here today.

Again, we have this document in April of 2006 and, as I said, we were aware of viral issues and so, in that guidance document, we did say that a full viral risk assessment should be performed and justified by the sponsor. Furthermore, the manufacturing process should be validated

for its capacity to remove or inactivate viral agents as recommended in ICH Q5A, a document on Viral Safety Evaluation of Biotechnology Products derived from cell lines of human or animal origin.

For those of you not familiar, ICH stands for International Conference on Harmonization. It really represents a consortium of regulatory authorities from Japan, Europe and the United States, together with industry counterparts that work together to harmonize technical documents and in this case on viral safety.

It should be noted that Q5A sets a very high standard for viral evaluations. It is the best reasonable assurance that the product is free of virus contamination, and this requires knowledge of how much virus may be present in the starting materials through validated viral test methods.

[Slide.]

Now, I think it is useful to talk a little bit more about this document and the control strategies that are described in that document. The basic line is that it is a comprehensive control strategy.

It doesn't rely on a single test. Typically,

animal-tissue source screening; if they are primary cultures, rigorous cell-bank screening for viruses that include viral specific test as well as general tests for virus; and a demonstration that viral clearance or inactivation by multiple robust orthogonal process steps, and demonstration that there is, in fact, excess capacity to clear viruses.

Finally, routine screening of cell culture harvest. And I think again the key is that these are all overlayers of control. We don't rely simply on testing, we don't simply rely on the fact that there is viral clearance properties of the manufacturing process.

We feel that in this case, the best way to mitigate it is have all these open controls for the process.

[Slide.]

Well, FDA's approach to this is that we recognize that ICH Q5A was meant for parenteral products, mostly of recombinant origin, not for orally administered or animal-derived products.

I think clearly, the risks associated with orally administered products is different than parenteral products. But one issue that we had was that we have actually no

guidance from FDA on orally administered, animal-derived products.

So our approach was to use sound science and risk evaluations and apply ICH Q5A where appropriate and that is to apply reasonable practices that minimize the risk to patient safety while ensuring that efficacious products are available and we seek expert guidance from this committee on the best approaches. This, in a sense, is a reality check.

[Slide.]

I would like to turn now to some of the viral risk assessments.

[Slide.]

I think before we do that, it is useful to define what risk means. Risk can be defined as a combination of the probability of occurrence of harm and the severity of that harm.

Typically, this risk severity outweighs the occurrence so that if, there is a severe event, we would like to see that the probability of occurrence is very, very low. We are as a society risk averse and I think the FDA takes that approach, too.

We talked about the risk to patients but, given

that we are talking about agents that might transmit an infection, caregivers and society's risks should also be evaluated.

Clearly, testing and a well-designed manufacturing process can reduce the risk of occurrence, and risk must be viewed in the context of benefit, a clear benefit versus a potential risk of uncertain magnitude.

An assessment of that magnitude of the risk is what FDA seeks from this committee, in addition to what things that might be useful to mitigate this risk even further.

[Slide.]

When the viral assessment is performed, FDA felt that it should include evaluation of the following criteria; the control of source material, the potential of viral species as human pathogens, the potential to do harm--in other words, with the potential input viral loads.

This was discussed in closed session, and the capacity of the process to remove or inactivate model viruses. This again was discussed in detail at the closed session. But, because these issues have a lot of proprietary information, I am not at liberty to discuss them

in detail here.

Of course, the impact that route administration has on viral safety. I think that if you note, the risk assessment here did not emphasize the risks of unknown viruses that might infect human populations. But this could be evaluated a number of ways and one of them is using these general viral tests like indicator cell lines and animal testing.

This will be a discussion I think point for the committee.

[Slide.]

Well, in terms of source material, there is control for PEPs. It is limited and limited by what we could theoretically do, for example, in the case of xenotransplantation.

Pigs are from U.S. and European sources. The pancreas glands are derived from pigs raised and slaughtered for food. No other species are slaughtered and processed at each facility, so the risks of cross-contamination with other animal species are minimal.

Slaughterhouses are regulated under the auspices of the USDA and European authorities. These regulations for

slaughterhouses focus on animal hygiene, source, veterinary records, surveillance of herds and documentation of feeds.

Good Manufacturing Practices for Drugs are not followed. But to try to implement that, given the number of organs that are used, would, I think, be impractical if not impossible.]

Organ quality is monitored at the receiving site and the other risk mitigation factors. The vaccination of pigs for PCV-2 or porcine parvovirus in some locations can reduce the loads of viruses entering into the process stream. However, these vaccinations are done for economic, and not for safety, concerns and it is our understanding that to try to get herds vaccinated totally would be impossible.

[Slide.]

Well, risk identification is what types of enveloped viruses could be present in swine tissues. And this slide shows a number of enveloped viruses and, on the next slide we see a number of non-enveloped viruses that might be found in swine tissues or have been found in swine tissues.

[Slide.]

But the real issue is what swine viruses are there that could cause harm so it could act as human pathogens. Here, you have a more limited subset of enveloped, non-enveloped, and the primary route of transmission. And, of course, when you have an oral drug, an oral route of transmission for a virus, there is a higher risk than a respiratory route.

Here, we have also estimated the occurrence of these viruses, and that is based on swine populations, the detectability of the disease and the target tissue tropism; for example, influenza virus, which may occur pretty frequently in swine populations, is respiratory transmission and restricted to respiratory tissues. Therefore, the occurrence in a pancreas is thought to be of low probability and the estimated occurrence would be very low.

In contrast, the foot and mouth disease virus is an oral route of transmission. However, through surveillance of these animal herds, it is unlikely that that virus would make it into the production process.

[Slide.]

The other sort of risk identification is swine viruses that are not known as human pathogens, and these

represent either unknown swine pathogens--and, of course, it is always difficult to test for the unknown. But an active animal disease surveillance program certainly would help, and so would additional in vivo or in vitro adventitious agent tests that are capable of detecting these types of viruses.

Again, we have questions for the Committee on these types of risk mitigation strategies.

The other type of risk is that swine pathogens that are not known to infect humans but are ubiquitous in pigs and may be present in the drug product. This would include the non-enveloped viruses, porcine parvovirus, porcine circovirus 1 and 2.

The reason for this risk, as you have heard, is potential to change species tropism.

[Slide.]

I think it might be nice to go into a little bit more detail on the risk assessment for porcine parvovirus and circovirus.

[Slide.]

I think regarding the risk, most swine herds have been infected with parvovirus. These are extremely

resistant to physicochemical treatment and withstand 100 degrees for 30 minutes, or you are not likely to inactivate it. Indeed, these viruses are also at risk for recombinant biotechnology products. But manufacturers in those processes put in nanofiltration units to clear the viruses.

Unfortunately, that is not feasible for this particular production process. So, in fact, it may not be feasible to revise the manufacturing process to achieve a more robust level of inactivation or clearance without compromising product quality.

Certainly, the elimination of contaminated lots by testing could result in the failure of some to many lots.

[Slide.]

Infectivity of parvovirus in humans and lower animals. In humans, it is very low, if not undetectable. Porcine parvovirus generally has been found not to infect human cells although there was one cell line that was infected by one strain of a virus.

Pig farmers who had been in close daily contact with parvovirus infected pigs for one year or greater were not positive for parvovirus antibodies. You heard of a factor VIII study that was contaminated with parvovirus and

those patients did not see a parvovirus related disease.

Consumers of pork products are probably exposed to live viruses but meat may have a different viral load. The consumption of pork products is clearly not associated with known diseases from parvovirus EZ. But the true impact of these have not been fully investigated.

On the other side, there are some risk considerations. As was mentioned, feline parvovirus has crossed species barriers to infect dogs and resulted in the deaths of many dogs back in the '70s.

Furthermore, the lack of studies evaluating the presence of antibodies to parvovirus in patients with cystic fibrosis using PEPs, so we really don't know what the level of risk truly is.

FDA is engaged in a study to screen patients with cystic fibrosis on long-term PEP therapy for antibodies to parvovirus and PCV-2 to better understand the risk that these viruses represent to patients.

[Slide.]

Well, in terms of severity, parvovirus in swine is pathogenic in pregnant sows. What the pathogenic potential in humans is is really unclear because what would constitute

human disease manifestations. But certainly a change in species tropism, is of great concern.

[Slide.]

Turning to 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 viruses could be expected to be present in the drug product depending on the specific manufacturing process, you expect more or less of that virus.

It has an oral/nasal route which is believed to be the route of transmission, and PCV has been shown to infect human cell lines. But mixed results have been reported for PCV infection in humans.

I think one study is that antibodies to PCV were reported in 30 percent of samples from hospitalized patients with fever of unknown origin. But the results have not been confirmed and there is some question whether those antibodies actually were cross-reactive to endogenous antibodies.

But I think in conclusion, PCV-2 may have a

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.

[Slide.]

Well, here we are worried about cross-species infections. But what are the realities of that?

I think an example from Simian immunodeficiency virus provides some sense of that. SIV counterparts of HIV-1 and HIV-2 were introduced into human populations at least 7 times.

The majority of human pandemics arose from only one cross-species infection, HIV-1 group M viruses.

Recombination between distinct viral lineages co-infecting a single animal are not rare events in nature. Indeed, if you look at the literature, it seems that these events pop up all the time, that they are much more common than we think they are, but that they just have a limited exposure to people in limited numbers. And then they disappear, sort of percolating apparently all the time.

Recombination, however, leads to altered tropism, virulence and drug resistance and it is not only from the

HIV example, there are examples from swine, influenza and recently Nipah virus, which are transmitted from bats to humans and we think there is also transmission from bats via swine and into humans, too.

So, these events are rare but they can occur. It is very rare for it to come to the level of a pandemic, but there are some instances where perhaps some introduction to human populations occur.

[Slide.]

Well, we thought it would be useful if FDA discussed a little bit about its risk versus benefit and its management of parvovirus risk. I would like to talk a little bit about case studies that illustrate our regulatory approaches towards parvoviruses, and we picked the human parvovirus B19 and the minute virus of mouse.

[Slide.]

In human parvovirus B19 pathogenicity, it commonly causes fifth disease, a self-limiting disease of children. Non-immune adults may develop a rash and/or joint pain. From what I have heard it is quite unpleasant.

Many cause transient aplastic crisis in persons with sickle-cell anemia and occasionally causes serious

complications during pregnancy. This is not a benign virus, it is a pathogenic virus.

[Slide.]

But what is the risk due to parvovirus B19 in human blood supplies?

Well, there is a high percentage of the human population that has been infected with B19 so rejection of blood units based on a screening test for antibodies, looking for the presence of antibodies in patients, could actually eliminate a large percent of the donors. I think it has been estimated that by age 70, 80 percent of the human populations have antibodies to B19.

Screening, therefore, of blood donations for the presence of B19 is currently not routine. We accept the risk based on the benefit and the difficulty in mitigating the risk any further. But FDA is clearly concerned about this risk and is seeking rapid tests to identify B19 in blood samples.

However, source plasma is screened for B19 and manufacturers have placed a limit of less than 10^4 genomic equivalents based on the information indicating that lower inocula have a greatly reduced risk of infections.

The conclusion is that we tolerate a relatively high level of risk for B19, a known human pathogen, because risk cannot be easily mitigated further without loss of blood supply. The benefit outweighs the risk.

[Slide.]

The other risk associated with the parvovirus is that of minute virus of mouse. This is a parvovirus that infects Chinese Hamster ovary cells which are commonly used to produce recombinant proteins.

There is no known pathogenicity in humans. But this is viewed as a contaminant that can be well controlled, and we do not tolerate in production streams--and recently caused a shutdown in production for two months of one biotech product.

However, there was no drug shortage that occurred with this as a result of this control strategy. In fact, most of the recombinant proteins are under this same type of control strategy, and we have never had a drug shortage that actually made us reevaluate the risk-benefit ratio.

If this was a medically necessary product and there was a drug shortage, then we would have to again revisit the risk-benefit ratio. But right now it's the

theoretical risk can be reduced to very small levels with appropriate controls with no impact to product availability, and we proceed with trying to mitigate the risk as much as we can. Again, it speaks to our aversion to risk.

The overall conclusion I think is that we accept a wide range of risk, based in large part on the ability to mitigate the risk to minimize the impact to public health.

[Slide.]

It also might be useful to talk a little bit about xenotransplantation, which raised serious public health concerns. After all, these are infectious agents from source animals that are actually placed in the body, so there is cell-to-cell contact in immunosuppressed hosts. So the risk for mutation, recombination and reassortment, and the development of an infectious agent with human tropism is there. It could be disease in recipient could lead to transmission to others.

[Slide.]

FDA's approach to risk mitigation for xenotransplantation is for source animals, stringent requirements for source animals and product testing.

Establish source animal facility barriers to limit

lifelong exposure of source animals. These are closed herds, to try to make pathogen-free herds. We are not trying to say that the risk from xenotransplantation is the same risk as we are talking about PEPs but still strikes some of the times the measures that we try to take when we do perceive a risk, infectious disease screening for the herd and source animals, and product-specific testing depending on the source species, testing types and geographically emerging viruses.

I think for the PEP products, the first bullet points are impractical. However, product-specific testing can be useful to help mitigate the risk.

For recipients, informed consent, education and counseling, surveillance of all patients, use of diagnostic tests, specimen and serum banking, to go back to tests if they see something and maintenance of health care records are all important.

[Slide.]

I would briefly like to talk about risk assessments because obviously, as I have mentioned, the capacity of the manufacturing process to clear or inactivate viruses is critical, and studies to determine the capacity

of the manufacturing process to remove or inactivate viruses were performed in accordance with FDA guidance by Solvay Pharmaceuticals.

They have demonstrated that there are two robust viral clearance steps that are present in the manufacturing process and the study showed the manufacturing process can inactivate enveloped viruses. But the process does not inactivate all non-enveloped viruses and shows moderate to limited inactivations.

These studies suggest that testing strategies should be employed to reduce these risks, particularly regarding certain non-enveloped viruses. We have had extensive discussions in the closed sessions about the strategies that should be employed.

I think we have received expert advice regarding both enveloped viruses and non-enveloped viruses but we are not at liberty to go through in detail on any of these discussions.

[Slide.]

The risk mitigation strategy also for swine viruses that are not known human pathogens. It is clear that porcine parvovirus and porcine circovirus are not

effectively inactivated by the process and live virus is likely to be present in some doses of pancrelipase.

Risk associated with these potential infections appears to be very low. But this risk could be further mitigated by testing for infectivity and thus limiting patient exposure, routine surveillance and monitoring for zoonotic events in patients treated with pancrelipase, to get a better idea and understanding of what the true risks are.

I would note that although Solvay Pharmaceuticals has mentioned now a surveillance program, this program is new to us, that we have not had adequate time to review this program. Dr. Pariser may like to make additional statements on that.

Additionally, better understanding of the risk by conducting appropriate studies elucidating the potential for transmission to humans, we think are warranted and, in fact, FDA, as we have described, has started to do some of those studies on their own.

[Slide.]

Well, another way of risk mitigation and I guess risk understanding, too, is better informed patients and

caregivers--for example, providing information to caregivers and patients on the risks. And you can read what types of things that we can put into a label are.

They also cover some of the issues that Solvay Pharmaceutical agreed should be communicated to potential patients and caregivers.

The other thing is to provide instructions if an infection is observed that might be related to the product; for example, if all infections thought by physicians possibly to have been transmitted by this product should be reported by the physician or other health care provider to a certain number.

This again provides more certainty about what the true risks are if we collect information and knowledge, and that is important in the regulation for these types of products.

With that, thank you.

DR. McGOWAN: Thank you very much.

We are going to take a lunch break now. I think originally, we had hoped for 60 minutes but, with a view to keeping on track, I am going to reduce that to 45 minutes. So we will reconvene here at 1:45.

Can I just remind the panel members that there should be no discussion of the issue at hand during lunch amongst yourselves or if any members of the audience.

Thank you.

[Luncheon recess taken at 1:00 p.m.]

AFTERNOON PROCEEDINGS

1:45 p.m.

Open Public Hearing

DR. McGOWAN: We are going to begin with the Open Public Hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have

any such financial relationships.

If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

The FDA and the committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect.

Therefore, please speak only when recognized by the Chair. I thank you for your cooperation.

We have three speakers this afternoon. Each of them will be given five minutes to address the Committee, and will be given sort of a warning at one minute to go so they can wind up.

The first speaker we have is Dr. Kenneth Attie from Altus Pharmaceuticals, if he would like to step up and give his presentation.

DR. ATTIE: Thank you and good afternoon. My name is Kenneth Attie and I am the Vice President of Clinical Development and Medical Affairs for Altus Pharmaceuticals in Waltham, Massachusetts.

By way of disclosure, Altus is developing a drug product called Trizytek or liprotamase, which is a biotechnology-derived alternative to the current porcine-derived pancreatic enzyme preparations.

The Trizytek drug product is a highly purified preparation of three carefully chosen enzymes for the treatment of malabsorption associated with pancreatic insufficiency, an amylase, a crystallized protease, and a crystallized and cross-linked lipase.

A product such as Trizytek carries essentially no risk of viral contamination or, for that matter, a sudden disruption of source material supply should a contamination be suspected in a swine herd.

A comprehensive Phase 3 clinical trial program of Trizytek is in its final stages. Earlier this year, Altus subm**itted a citizen's petition to the FDA pertaining to the review or approval of porcine-derived pancreatic enzyme products.

In the petition, we requested that biosafety risk management be addressed and, in addition, recommended that class labeling be implemented to inform health professionals of the risk, if any, of potential adventitious viral agents.

In view of the apparent inability of manufacturers to fully comply with ICH guidelines that require viral clearance and/or viral inactivation procedures, we further propose that warnings be provided to consumers similar to those implemented by FDA's food code for the risks proposed by eating raw or undercooked pork.

The FDA Amendments Act of 2007 requires that manufacturers exercise greater diligence in assuring timely inclusion of safety information and requires that the Agency implement risk management plans in connection with new drug approvals to assure that risks and benefits are properly weighed and understood.

In the case of porcine derived pancreatic enzyme products, the Agency must strike a balance between the need for access to therapy, on the one hand, and the time and effort needed to perform adequate product characterization, manufacturing controls and clinical safety studies on the other.

Consistent with the requirements of the FDA Amendments Act of 2007, we support the Agency's decision to convene this Advisory Committee meeting today in connection with the review of products in this class to determine the best approach for risk management and to protect the patient safety.

The existence of a non-animal derived product in late stage development, such as Trizytek, we believe is relevant to today's discussions. It is clear that the risk of viral contamination at this time is a potential risk with health consequences that are unknown.

The same could be said for the safety evaluation of any drug product before appropriate manufacturing processes are implemented and adequate clinical safety trials are completed.

As a pediatric endocrinologist, I am reminded of the catastrophic and tragic case of pituitary growth hormone before the approval of recombinant growth hormone in 1985. Despite the best attempts at the time at purifying cadaveric pituitary extracts prior to treating thousands of children with growth hormone deficiency, the worst case scenario came to pass and nearly 200 of them have contracted Creutzfeldt-

Jakob disease, which is uniformly fatal, due to the transmission of a pathogen from those extracts.

This experience alone tells us that extracts of animal organs that are not subjected to validated procedures to remove or inactivate potential pathogens should be a last resort as a source for human drugs.

Even a suspected contamination can cause loss of herds of animals and potentially disrupt the supply of source material for these life-saving therapies.

Altus, along with the Cystic Fibrosis Foundation, and concerned investigators from around the world, undertook the long process to develop a modern alternative to a drug class that is currently archaic by a host of standards.

Until such time that we can bring such alternative therapies to market, we hope the Agency will adopt procedures to reduce the risk of viral contamination of porcine derived pancreatic enzymes and provide adequate warnings of any such risks to help professionals and consumers.

Thank you.

DR. McGOWAN: Thank you very much.

Our next speaker is Jane Holt, who is the co-

president and co-founder of the National Pancreas Foundation.

MS. HOLT: Good afternoon. Thank you for allowing us to speak today. As you have said, my name is Jane Holt and I an co-president and co-founder of the National Pancreas Foundation.

The National Pancreas Foundation for all of you who don't know is the only organization that takes care of the patients with all diseases of the pancreas including acute pancreatitis, chronic pancreatitis and pancreatic cancer.

But I am not only here on the part of the Foundation and the patients with chronic pancreatitis, I am also a patient with chronic pancreatitis, and I have been greatly helped by enzyme supplements. My purpose today is to present a face for the patient suffering from pancreatic disease.

Twenty years ago, my life was turned upside down when I was awakened in the middle of the night with intense pain in my abdomen. The pain was unrelenting. I finally found my way to the emergency room and six to eight months later was diagnosed with chronic pancreatitis.

Chronic pancreatitis changes your life. You can no longer freely eat whatever you like, whenever you like, or as much as you like and, if those restrictions weren't bad enough, there is a twist. When you do eat, your body can no longer derive all the nutrients it needs to keep you strong and healthy.

As has already been mentioned, pancreatic patients have difficulty absorbing four important vitamins - vitamin A, which affects how we see, malabsorption of vitamin D renders pancreatic patients vulnerable to osteoporosis and bone fractures and vitamin E's suspected role in the body's immune system is essential for good health. Vitamin K plays a vital role in blood coagulation and enzyme supplements help patients mitigate their exposure to these dangers.

But even more importantly, enzyme supplements have made pancreatic patients lead a more independent life. Think about it. When your body can't absorb the fuel it needs to run properly, you become weak, you lose too much weight, fatigue sets in, all which conspires to make it almost impossible to have a full-time job.

If the body can't absorb these nutrients, where do they go? They pass quickly through the body and are

released in the form of diarrhea and also steatorrhea, which is basically a stool which has too much undigested fat in it. This, too, makes it difficult for pancreatic patients to participate fully in professional and social activities.

Worst of all, and this is the most heartbreaking one for me who developed pancreatitis as the mother of four young active children, pancreatitis and its attendant pain, discomfort, fatigue and illness, results in multiple annual hospitalizations.

Children don't understand why their mom or dad has to always be in the hospital and miss their school play or their big game on Thanksgiving morning and, of course, we simply do not want that to happen either.

At NPF, we receive phone calls and e-mails from patients all over the country and all over the world. More often than not, these calls are not happy calls but complaints about the problems that they have with their diseases and, although this is certainly not a scientific study, we have never received a complaint about pancreatic enzymes or infections from these enzymes.

On the contrary, most patients remark about how helpful pancreatic enzymes have been. Pancreatic enzymes

are really all the patient with pancreatitis has. Doctors can only treat our symptoms. Pancreatic enzyme supplements are not magical and they will not stop us from having to be hospitalized occasionally but, for many pancreatic patients, it helps us to lead a more normal life.

When I spoke to my doctor and asked him what his thoughts were if he was told he had to stop prescribing enzyme supplements to his patients, his answer without hesitation is that it would be a terrible thing. Speaking from experience and from all the patients that I know have who have chronic pancreatitis and we hear from, we all really agree and we hope that you, today, decide that pancreatic enzymes are a very important item for the patient with chronic pancreatitis.

Thank you.

DR. McGOWAN: Thank you very much.

Our final speaker in this section of the meeting is Tibor Sipos, who is president of Digestive Care, Inc.

DR. SIPOS: I would like to thank the committee to give me the opportunity to speak here. I am, as said, the president of Digestive Care, Inc.

Digestive Care is a small, privately held

pharmaceutical company and we are manufacturing and marketing an innovative enteric-coated and buffered pancrelipase product called Pancrecarb since 1995.

I have listened carefully to several of the previous speakers and most of my questions have been partially answered and, obviously, I am waiting anxiously for the Committee's decision what type of recommendation they are going to have in terms of the viral assessment measurement and abatement of the viruses present in the pancrelipase preparations.

Therefore, the reason I would like to just truncate my comments and thank the Committee to give me this opportunity.

DR. McGOWAN: Thank you very much.

The open public hearing portion of this is now concluded so we will no longer take comments from the audience.

Advisory Committee Discussion

DR. McGOWAN: The Committee will now turn its attention to address the task at hand, which is the careful consideration of the data before the Committee, as well as the public comments.

I just need to remind you again that we will begin the panel discussion portion of the meeting and, although this portion is open to public observers, public attendees may not participate except at the specific request of the panel.

Now, in terms of the process and the voting procedures, we did have a trial run this morning and we now have another opportunity.

Basically, just to remind you, if you needed reminding, we will be using the electronic voting system. We have four questions. I will introduce the question, we will then have a discussion, there will then be a vote. The vote will involve the technology that you have in front of you. You will notice a yes/no and abstain button.

Once we begin the vote, please press the button that corresponds to your vote, and you will have approximately 20 seconds to vote.

After everyone has completed their vote, the vote will be locked in, the vote will be displayed on the screen, and then I will read the vote from the screen into the record.

Next, we will go around the room and each of you

needs to introduce yourself with your name and then state your vote. Then, there may be some subsequent activity. You may be asked to comment on some aspect of the question.

After the discussion, that will be that. We will have a discussion after I have presented each question, I will end it, and then we will move to the vote.

I think now I need to pass over to my colleague, Anne Pariser, again from the Division, who will outline our responsibilities.

Charge to the Committee

DR. PARISER: Thank you, Dr. McGowan and members of the Committee. Just to restate the purpose of this Advisory Committee, we are here to discuss the viral issues associated with the PEPs and the theoretical risk that porcine viruses posed to the patients.

We acknowledge that the PEPs including Creon are medically necessary products and we do not feel that this issue is in dispute.

You have heard today details on the source of the materials from swine, a discussion of the manufacturing process and the inability of that process to completely eliminate live virus from the products without completely

destroying the activity of the enzyme.

Although the viral risks to patients appear to be low, they are not zero, and cross-species viral transmission can and does occur sporadically. There are despite the long history of use of the PEPs, there have been limitations in the available safety information with the PEPs and these limitations are known.

Although they have been used for decades, PEPs have not been available under IND or NDA prior until recently so the safety reporting has been really minimal.

Although it is unlikely there have been large outbreaks of disease because of the PEPs, we really can't say much more than that. There is an absence of prospective data on infections or on serum monitoring in patients in the clinic and, although cases have not been reported in the literature, that does not mean they have not occurred.

It becomes particularly difficult because the population, such as the CF population, has a high background rate of infection, making it difficult to detect sporadic cases.

So moving forward from today, what we are asking the Committee's advice on is how to mitigate those risks

that does exist.

Questions to the Committee, which you will be seeing shortly, or asking to vote on shortly, include what product testing is necessary and specifically what do you recommend. Is animal surveillance necessary? What additional measures and manufacturing process do you recommend to mitigate this risk?

Is viral risk identification and evaluation in patients needed and should patients and physicians be informed of viral contamination?

Just finally, we would like to say that Solvay has presented proposals for both prospective and retrospective patient monitoring today. We would like to say that we have not seen this prior to today, so we have not had a chance to review this and evaluate this and we very much look forward to hearing the Committee's comments on these proposals.

Thank you.

Advisory Committee Discussion

DR. McGOWAN: Thanks very much, Anne.

Following that, we will now move to the first question, which you can see in front of you. The question is that the risk of cross species infection associated with

the presence of PPV or PCV in the pancrelipase product appears to be very low but could be further reduced by testing for infectivity and ensuring limited patient exposure to these viruses.

In that light, should testing for infectious PPV and/or PCV 1 and 2 be conducted for pancrelipase batch release testing?

I would like to open this for discussion amongst the Committee, if they have any thoughts, comments, or questions for clarification.

Dr. Havens.

DR. HAVENS: We have a parvovirus expert in the audience, or at the table here, and I would love to hear about the real risk to humans from this porcine parvovirus and then concerning the PCV 1 and 2, we also have some expertise at the table.

I would really like to hear about the issues related to the potential for human infection from these viruses, because I think part of the answer here is, is there really an identifiable risk to humans that we care about.

Another part of the risk that we have to evaluate

is what has been discussed concerning patient acceptance of these products. It would be terrible to say, to get everybody too scared to take drugs that are very important for them to take.

So, then to Ms. Holt, I would love to hear her perspective on if she thinks people which call her would rather know that the viruses are there and looked for, or would rather pretend the viruses weren't there or is the cat out of the bag already and so we ought to just deal with it.

I have I guess three questions, one for parvovirus and PCV, and for the patient response from Ms. Holt who I think has a special perspective on that.

DR. McGOWAN: Do we have a parvovirus expert?

DR. THACKER: Well, I think for that, Colin, you probably have more experience with changing of different species amongst the animal world. For parvovirus, I have done quite bit with PCV 2 and PCV 1.

Let me just take a couple of minutes to talk about these two viruses, because they are newly emerged as far as PCV 2 into the swine world as far as causing disease although they have been there for many, many years as a matter of fact, when they look back, it has been in swine

population as long as we can look in tissues.

Again, something within that virus changed to make it cause disease in pigs. Exactly what that was or why that is, we don't know. The thing with viruses, as I am sure Colin and anybody else will support, is they are unpredictable as to their changeability at some points.

So PCV 2, PCV 1, PCV 1 is non-pathogenic even in pigs and has been around forever in cell culture. PCV 2 has been newer, has only really started causing disease within the last five years in the United States swine world, and so it is kind of a difficult virus to really predict as far as exactly what it is going to do.

Today, in my lab, I did research on PCV porcine circovirus and, as far as I know, none of us have ever had any problems and, as far as I know, there has not been a case of PCV going into humans. But that being said, you can't say it is without risk at all.

So, from my perspective and working with the swine viruses, PCV 2 is a little more of a question because of the short duration of disease.

Now I will turn it over to somebody else to get their perspective.

DR. PARRISH: I am Colin Parrish and we do study parvoviruses in their host ranges. And this is a little bit of a thing that I haven't completely prepared like a presentation on, but I just wanted to sort of touch on the fact that there are a couple of issues going on here.

One is the issue of sort of host switching and that is about how do viruses change from having a host range in one species to another, which is what we are really talking about.

This is often considered to be sort of a dramatic event. When it occurs, it's actually a very rare event. We wrote a review recently where we tried to look at sort of the issues around host switching, how they occurred and what the circumstances were. And it is pretty clear that we could really only identify a handful, half a dozen or 10 or so, examples where viruses had truly changed from one host to another, not to cause a single infection but to cause an outbreak and then go on to cause an epidemic.

So, there are clearly, you know, in the context of host switching, there are viruses that you can become exposed to viruses. We get exposed to viruses every day from all sorts of species of animal that we come in contact

with. I am including ones that we don't even know about but that are in the environment around us.

Occasionally, those cause disease in humans. Those are called genoses, and they are often seen as a single infection. Very occasionally, those will go on and cause an outbreak, probably only a very small percentage of those host transfers cause an outbreak of any sort even from one person to another.

Then, the very, very rare event is the one that goes on and causes an epidemic or larger outbreak. So, you have got to look at it as there is sort of a very low probability that any virus which is well adapted to its current host is going to be able to cause an infection in another host.

We do know in the case of the swine viruses that humans have been exposed to these viruses including the circoviruses and the arteriviruses that also affect swine. Although they are the cause of relatively recent clinical disease in swine, it is clear that they have been in swine for many, many years, probably hundreds of years, and almost certainly people have been exposed to them in very large amounts during the farming, processing of meat and

consumption of meat.

I think we have to remember that when we are exposed to swine, you know, we don't just eat the muscle. People have traditionally eaten a number of different organs, and I am guessing that we have been exposed to very large amounts of most of these viruses over thousands of years and in at least some populations and some cultures.

So, I think we have to look at the fact that, you know, I am just trying to put this into sort of a perspective, you know, individual transfers may occur, that they are still relatively rare.

The ability of a virus which has been exposed to humans for many years to go on and cause a new disease is, in fact, something that is virtually impossible to predict. But that almost certainly would require multiple mutations. In the case of the virus that we study, which is a parvovirus of cats, which transferred into dogs, which is obviously a closely related animal species.

It took, we think at this point, about 6 or 7 mutations in the virus, and not just mutations of any sort but very specific mutations which had to occur in synchrony at the same time or in very close and a very specific order

for the cat virus to become adapted to dogs. It did go on and cause an epidemic of disease but, as far as we know, it is really the only example that I know of of a parvovirus that transferred from one host to another.

We don't have any indication that other parvoviruses are, for example, particularly prone to transfer between animals. It is not like influenza, which is often seen to, for example, transfer from one animal to another, at least under relatively--you know, every decade or so an example is identified.

In the case of the parvoviruses, this is really the only example that I am aware of. What is the probability of gaining this group of mutations that allowed a virus to go on and become, in this case, an epidemic in pandemic virus?

We think the probability is probably the sum of the number of specific mutations. So that could be on the order of 1 in 10^{30} or some number like that, a very small probability.

We do know something about the susceptibility of human cells to porcine parvovirus. There is one example alluded to of that virus called KBSH, I think, which was

found in a human cell line. It was adapted to human cells and had a number of mutations which made it able to grow in human cells.

That virus as far as we know is not infectious to humans. It certainly doesn't replicate in humans as far as anyone knows. There is no evidence at this point of--no one has identified antibodies to parvovirus in people who are exposed to swine either through farming or through processing of meat so it does seem that the barriers to transmission of the peak parvovirus in humans are probably relatively high. Probably if the virus could adapt to humans, and we have no way of knowing whether it can, the probability is that it would take several or more mutations for it to do that.

I am just trying to sort of again put things into context of what we know about how viruses transfer host ranges and also how parvoviruses adapt.

We do know parvoviruses have a relatively high mutation rate for DNA viruses, and this may also be true for circoviruses as far as anyone can tell.

They certainly show some variation in their sequences. But they are not extraordinarily variable and we

think that, again, the probability of any particular group of mutations occurring and being selected is a relatively very low probability.

I am not sure if that is clear--but if there are any questions or if I can help to explain anything else.

DR. THACKER: I would like to bring up one other thing about both of these two viruses is they are very, very, very much ubiquitous within the swine populations.

The chances of you being able to get pigs that are not parvovirus positive, that are not PCB 2 positive, are just about zero. So to ban this product at this point in time based purely on finding the PCR-positive would probably be very difficult to do.

I believe last year or the year before they did do a serological survey of veterinarians at the American Association of Swine Veterinarian meeting, which are people that work with a great deal of swine, and did not find evidence of circovirus antibodies.

These are people that work with large numbers of pigs samples, they would be very intimately associated with a virus, and there was no evidence that humans were infected.

So, that is my and Colin's perspective on these two swine viruses that don't cause--circovirus is kind of different because it will cause disease but not consistently.

DR. ROSENBERG: I would like to make a statement, and that is that at this point we are not at all considering banning or removing these products. We are just trying to mitigate risk and get an understanding, a better understanding, of what that risk is.

This is very helpful, but just no consideration of banning here.

DR. THACKER: I just wanted people to be aware that these viruses are ubiquitous within swine. I mean I did research on PCB 2, and I could not find a negative herd, period, anywhere in the country.

DR. PARRISH: I might talk to the ubiquitousness. Both of these viruses do cause an acute disease and at least initially in the case of the PCB 2, the circovirus 2, the disease is often associated with secondary infection, often by another virus or sometime mycoplasma of a pathogen. But the levels that are found in most swine are relatively low. They have very high titers at times during the acute phase

of the infection.

The residual virus that is seen after the animals recover, which is normally within a few days in the case of the parvoviruses, and clear the virus by antibody and other immune responses, is, in fact, relatively low and probably reduced by 10^6 or more compared to what the levels were during the acute phase of the infection.

So, the tissues in the pancreas, at least in the case of parvovirus, is not normally a tissue that the virus targets. They only replicate and divide in cells, and I suspect that is true for the circoviruses.

In an animal that is older than a few weeks old, the pancreas is not a tissue that has many dividing cells in it. So, I think that relative levels are going to be low to start off with.

If you had a fetus, you know, in the case of a parvovirus, the fetal infection, can, in fact, have enormously high levels of virus. Those sorts of numbers really don't have anything to do with the kinds of tissues that are being used in this case.

I am not trying to sort of reduce, you know--I am not trying to say anything about safety in a specific way

but just to say that the levels, in fact, are very low in the tissues and organs that we are looking at here, I think, compared to what there are in other circumstances.

DR. HAVENS: There is some CDC expertise in this are; specifically, is the human parvovirus the same as the porcine parvovirus that we are talking about, or are they really different.

DR. ANDERSON: They are totally different viruses.

DR. HAVENS: Thank you. That is very important.

DR. ANDERSON: Most of the parvoviruses are really species specific and, as Colin noted, they usually don't cross species with the one exception that he talked about.

It gets a little bit into the virus looking for disease, and you have got a pathogen and what do you do. I think all the evidence would suggest that you are not getting infection. You don't have all the evidence that could help you think about that.

I think looking at CF patients for serologic evidence of the virus is of interest, would make some sense. If you find infection, you still don't know if it causes disease, which is another issue, so there is a sequence of things here that come into play.

Then, the question becomes should you screen with the idea that it causes no harm and it may be good. Well, it is not quite as simple as that because I think, when you get a positive, you really do have to understand and think about what you are going to do with that result. And is it really important to screen out of ours that from everything we know, and we don't have all the information, does not actually cause infection or disease in human.

Those are some of the issues underlying the questions that we are talking about.

DR. HAVENS: Now, can I reformulate my question for Ms. Holt. Hearing from the specialists in virology that, number one, the parvovirus in pigs is dramatically different than parvovirus B19 that is found in humans, number two, that there is no specific disease in humans that has been attributed to these porcine viruses that are asked for in this specific question, would you and patients that you potentially speak for feel more comfortable if you knew that the pancrelipase product that you were using was being screened for these and a low level identified that FDA and the company, for example, felt was low, or would you feel better without screening, given the fact that the cat is out

of the bag, that these porcine products, which are crucial and currently available, have now been identified as being different than the potentially available recombinant product but this is what we have got now and this is what people need.

Would you rather have these things screened for and identified as present and potentially at low level, or at a level that people agreed on, which might be somewhat arbitrary, or not screened for at all?

MS. HOLT: One of the things that I am thinking as you are asking me these questions is that for most patients with chronic pancreatitis, pancreatic enzymes are helpful, and the patient with chronic pancreatitis knows that.

But one of the problems that we find with our live support groups, our on-line support groups and calls we get, and I have to even admit with myself is that we don't take our pancreatic enzymes as we should necessarily.

I just had lunch and didn't have pancreatic enzymes with me and didn't take any. So, there is a large part of me that does not want to cause any of the patients to be less likely to take these enzymes.

They help us and if it's a very, very slight case,

which is what it sounds like, my gut leads to encouraging the patients to take the pancreatic enzymes because they help them, and the chances of an infection seem to be very, very rare.

I know that we spend a lot of time telling patients they should be taking these enzymes, and I would hate to have somebody have a reason to not do it.

DR. McGOWAN: Having said that, though, I think, as these products move towards an NDA and a package insert inevitably, as with all drugs, there will be a list of potential risks and benefits laid out in graphic detail.

I think most clinicians and, to a variable extent, patients accept that package. They need the drug. They will be hopefully cognizant of whatever risks there are. But this is an evolving story.

At this point in time, if we do--I am going to come on to this later, but if we do address package insert language, what can we say. There is a risk of these viruses being present. At this point in time, there is no evidence they represent a significant or even a health challenge to humans.

That may change, but that's where we are at the

moment I would think.

MS. HOLT: Yes, and I also would like to add to that almost all of the medications that I take, if I read those completely, tell me I have the chance of getting abdominal pain from whatever I take. Granted, I don't listen to that either.

DR. McGOWAN: Okay.

Over to Dr. Chapman on my right.

CAPT CHAPMAN: I would like to hear some discussion about the exact wording of this question, because the question asks us about our opinions about testing for infectivity of these viruses.

Given that the FDA has made clear that they do not see removing a product from market that is critical to a large population of patients as anything they intend to do, and I haven't heard anyone on the committee say anything that sounded as if they would be inclined to vote to remove a product because present in it are viruses that are ubiquitous in the pig population from which it is derived, I am not sure this is the right question.

It seems to me there are two reasons to consider. And I am not advocating this. I am putting it on the table

for discussion to consider whether you would want to test for these viruses in the batches even if you believe they pose no risk of infection, neither of which in my mind would involve testing for infectivity, would involve testing for quantitative presence.

One is FDA has made comments or I thought I had heard comments about interest in testing that would help, that the purpose of bringing these products under FDA regulation is to move to a better standardization of the safety and efficacy and validity or, you know, standardization from batch to batch of these products.

I have also heard the question raised earlier and I think that there might be some consideration as to whether something in the manufacturing process might--clearly, we have looked at eliminating viruses, but also whether it might concentrate viruses.

So, with those things on the table, it seems to me there are two reasons to consider quantitative, say, testing, PCR testing of batches for the presence of these viruses.

The first is to document standardization or absence of standardization from batch to batch in viral

presence, which would speak to quality control issues. The second would be to maintain an ability to observe over time going forward whether--if there is, in fact, variability among batches whether higher quantitative levels of viral DNA in specific batches correlated in the future with symptomatology in patients.

I guess I would be interested in hearing some--both of those are a little different than the way this question was framed, and it is not obvious to me that if you thought either of those was a valuable reason for testing, you would want to go on and incur the further expense of infectivity testing. But I guess I would like to hear some thoughts on whether either of those would have value.

For the second, if the reason for testing is to quantitate viral load per batch, and to see if that correlated with symptomatology in patients in the future, then, I guess the question that would raise is if someone thinks that is a good idea, should that be done as a limited investigational study, or should that be done as part of regulatory policy.

DR. McGOWAN: My problem seems to be that neither of these viruses are transmissible to humans. So, if I

understood the first part of your question, you are alluding to using quantification of viral presence and correlating of symptomatology but it hasn't crossed into humans yet. So did I misunderstand you?

CAPT CHAPMAN: No, you didn't misunderstand me. One thing that seems to me like one thing I don't understand why we are not hearing data on is given that we have heard that there are something like 5 million patient years of human beings exposed to these products, presumably all of them replete with parvovirus and porcine circovirus, I am a little--I am wondering why we aren't hearing the results of serologic testing of those exposed patients for evidence of past infection with these viruses.

Is it not feasible to sort out serologically whether you are looking at infections from these viruses or human correlates, or has that study just not been done?

DR. ROSENBERG: I should tell you that that is something we realized was an important factor, too, and FDA is undertaking those studies now.

DR. McGOWAN: Next on the list is Dr. Clay.

DR. CLAY: I guess the question I had for Dr. Parrish and perhaps Dr. Meng, you have got the most

experience with these viruses, do you have any concern or have you ever considered within your laboratory to do any seroprevalence testing of your personnel.

DR. THACKER: No. To date with these viruses, we don't. Historically, I did influenza research and we always made sure our people were well protected for influenza, because we know that they will pick that up, and even that was not too much. But no, no; we have never really seen any evidence within the swine world of cross spreading with porcine circovirus type 2 or parvovirus.

DR. MENG: I just want to add to Dr. Thacker's comments. There are so far two serological studies in humans. One, I think is mid-1990s, and that reported detection of antibody to other porcine circovirus presumably type 1.

However, a recent study by John Ella's group from Canada could not confirm that study, and the common impression, understanding in the scientific community for this virus, is that the early study is probably detecting cross-reaction epitopes.

Also, I should add here that most of the swine herds now are vaccinated against this virus. There are four

vaccines available including one developed by us, and all those vaccines are on the market. This is a ubiquitous virus and there is no evidence of human infection at this point.

DR. McGOWAN: Dr. Parrish wanted to talk about his approach in his lab.

DR. PARRISH: We don't consider it to be a risk in terms of the exposure in the laboratory specifically, and I would say that for the canine parvovirus, and I think this is also true for the porcine parvovirus, basically, we consider them to be ubiquitous in the environment. Any veterinarian, anyone who owns a puppy is probably exposed to more virus than they really want to know about.

In the pig world, I am sure that the viruses are present. When you have a pig-rearing facility in any country of the world, whether you vaccinate or not, you basically are going to be exposed to the virus in I would guess much larger quantities than any patient is going to be exposed to it in the case of these products.

We have no quantification about that, but these are viruses that are truly ubiquitous in the environment. Any animal, any pig farm that you go to is basically

considered to be infected, and I think that is true for all these three viruses.

DR. THACKER: You can see that because influenza is transmitted between the workers and the pigs both ways, and we have done research on that and shown that. So, that is a truly zoonotic virus, whereas, these we have seen no evidence.

DR. McGOWAN: Dr. Ferry.

DR. FERRY: I can see the rationale to learn more about these infections and perhaps how commonly you can actually find evidence of the virus and whether it's infective or not. But right now I don't see enough information to apply that to patients at all.

I mean I think the information would be helpful. But right now to make it regulatory, then, I am going to have a hard time thinking what are you going to do with that and what are you guaranteeing.

So, the question sort of includes ensuring limited patient exposure. You know, it could turn out that you pick up evidence by PCR all the time that these are there, and maybe that has been true for 50 years or however long the viruses have been around.

It doesn't seem to me that we are at a point that we can make very much out of this, and the fact that they haven't crossed over to humans so far, it's a pretty low risk, I think it needs to be studied. But I am not at a point where I would say it needs to be put into regulations.

DR. McGOWAN: Dr. Kercsmar.

DR. KERCSMAR: My question was regarding the study the FDA is engaged in to look at antibodies for these viruses in CF patients. Can you give us a little more information on that, and what the time course is or when any data could be expected from that?

It sort of gets to I think Dr. Chapman and Dr. Ferry's point.

DR. RAGHEB: As was mentioned earlier, there is no existing assay for detecting human antibodies to parvovirus, and that would be one reason why investigators haven't looked in their labs. But these are not available.

So, we are in the process of developing such an assay qualifying it, eventually validating it and, if it hopefully works out, we will be able to screen. Our intention is to screen serum from CF patients for the presence of antibodies.

Some of the issues to contemplate would be because our concerns with these products in terms of the limited viral load that the hemophiliac patients would have experienced from intravenous administration of the PTV-contaminated clotting factors or the casual or passive context of swine workers is the potentially greater amounts of virus that somebody would encounter through the oral route over many, many years of exposure.

So, there are issues in terms of whether these studies should first be conducted in adult patients who have been exposed to these products for many years. On the other hand, conducting studies in pediatric populations gives us the opportunity to test serum before and after initiation of therapy which might be helpful in distinguishing false positives.

But I think some of those things can be addressed by techniques such as Western blot. Hopefully, within a year we would know.

DR. McGOWAN: Dr. Luque had a question.

DR. LUQUE: My question has to do with vaccination. Is a vaccination required for all the herds? Somebody mentioned parvovirus vaccine and also circoviruses,

is there a vaccine for that?

DR. THACKER: There are vaccines. Parvovirus vaccines are given for gilts because parvovirus causes abortions and problems reproductively for gilts. So, in most swine herds, those are the only animals that are vaccinated and then immunity to parvoviruses is often life-long. So that is going to be one question that I have, is when you find antibodies, what does that mean.

As far as circovirus, there are fairly new vaccines, but they are very effective. They not only pretty much reduce clinical disease--oh, very, very much--but they also reduce the viral load within the pigs. So they are finding the viral load on a herd level as they vaccinate these pigs.

Because of the economic importance of this disease, I would say at least 80 percent of the pigs in the United States are vaccinated for circovirus now.

DR. McGOWAN: Dr. Anderson.

DR. ANDERSON: In terms of screening patients for risks of infection, what about hepatitis C virus, I mean there is a virus that we know can be zoonotic, we know it has been present in these preparations and, as far as we

know, clinically, at least, I don't think there has been any evidence of hepatitis C virus infection in recipients that has at least been noted.

A second part of that question is, even though it is not completely inactivated in the course of producing a product theoretically, is it possible that if it is present in a product, and at the time it's released in the GI tract the concentration of enzymes, whatever is such that it inactivates the virus further?

I mean I am kind of surprised that there is no at least clinical history of hepatitis E virus being transmitted with this kind of product if it's there in any degree, which I guess is it fair to say it's likely to be present at some level.

DR. McGOWAN: Dr. Havens.

DR. HAVENS: Could we ask the company to comment on that specific question? So, the question would be has the company screened for hepatitis E, and has the company found hepatitis E virus in their preparations and if they have found that in their preparations, have they kept that from market or not.

I guess that would get to what Dr. Anderson is

asking in terms of the potential for potentially infectious material to get into humans. From the perspective of CF, liver disease happens in kids with CF, and so if you are going to get a mild elevation in ALT, if you are just looking clinically, you might not notice it.

So, that would be an issue. But from the perspective of the company, I think those would be three questions I would be interested to hear if they want it or if they didn't want to comment.

DR. SANDS: Part of this is reference to our closed conversation this morning and proprietary information.

DR. HAVENS: No, I am only asking anything you want to say in open session. I am not asking you to say anything you don't want to say in an open session, sir.

DR. SANDS: Thank you.

I tried to recollect the question. So if you could reiterate one more time and to make sure I have it right.

DR. HAVENS: The question as I understood it from Dr. Anderson was if there had been the opportunity for patients with cystic fibrosis to be exposed to hepatitis E

virus, then we might have seen some disease. That would be one question.

The clinical screening of patients with cystic fibrosis for symptomatic disease from my perspective is very difficult to get a meaningful signal from, because there is already a significant amount of elevated transaminases in patients with cystic fibrosis.

So, then if you think that the clinical screening is not appropriate or not a good way to find a signal, then, you have to go to the other end of the problem, which is the drug. So, then the question is has the company screened for hepatitis E, if the answer--and I only want you to answer things that you want to feel comfortable answering in an open forum.

I am not saying anything, I am asking questions. If you can choose not to answer them, that's your prerogative I think. The question is has the company screened for hepatitis E. If the company has screened for hepatitis E and found it, then, has the company made a decision not to allow that drug to go forward on to market because then that would partially answer Dr. Anderson's questions about why there might or might not have been

hepatitis E found.

DR. SANDS: Thank you for clarifying. I can answer that question very comfortably. Yes, we have screened for hepatitis E and, yes, we have dealt with material that has been positive for hepatitis E.

DR. HAVENS: Have you kept it from going to market?

DR. SANDS: Yes.

DR. HAVENS: The follow-up question to that is, is that in the to be marketed product or the currently marketed product, because as I understand from page 20 of your handout for the open session, the Creon currently marketed product is actually made by a different company SPL, not made by Solvay.

So, the question then is, does that concern the currently marketed product or the to-be marketed product, because those are made by different companies, as I understand it.

DR. SANDS: Dr. Rueffer will address that for you.

DR. RUEFFER: In the currently marketed product, as already has been said, the pancrelipase used is from a different manufacturer. But we apply the same testing as to

our produced batches.

DR. HAVENS: Thank you.

DR. McGOWAN: I would like to take one last question on this discussion from Dr. Chapman, and then I think we have to sort of move towards a vote, because we do have a lot of other questions to address in the time we have allotted.

So, a last question or comment?

CAPT CHAPMAN: Not really a question. Given that it has been stated by the company that they have tested for hepatitis E and, if they find it, they don't send the product out, it seems to me Dr. Anderson's question has to do with people who may have been exposed at some time in the past when such testing wasn't done and that's a very easily answered question, and you do it by taking cohorts of people who have been exposed to this product in the past and cohorts of matched controls who haven't been exposed in testing for prevalence of antibodies to hepatitis E.

I mean that is something that could be laid to rest pretty easily I think. I don't think you can answer it clinically because the people who take this product have ongoing clinical symptoms that are going to be

indistinguishable clinically from mild viral hepatitis infections.

DR. McGOWAN: Great. So, at this point, then, I would like us to move towards the vote, which essentially addresses the question should testing for infectious PPV or PCV 1 and 2 be conducted for batch release testing, and it's a straightforward yes or no question.

So, if you could vote no or abstain, I am sorry, yes.

[Electronic voting]

DR. McGOWAN: Just to read into the record, then, Question 1a. We essentially have 6 people saying Yes, 10 saying No, and no one abstained from this question.

Question 1b is really a subgroup question now. So, for those folks who said Yes, I need them to tell the Committee which viruses should be tested. Should we be testing all of them or 1, 2, or 3.

If we can go around the table and those individuals who said Yes, if they could let us know what their recommendation would be.

Let's first of all do the administrative thing, which is to go around the table and give your name and your

vote, and I think at that point we can use that as the opportunity if you say Yes, what viruses would you like to be tested for.

So, if we can start with the first voting member, which I think would be Dr. Ferry.

DR. FERRY: George Ferry. No.

DR. PARRISH: Colin Parrish. Yes. I would advocate testing for the three viruses.

DR. CHERNICK: Milica Chernick. Yes for all three viruses.

MS. ARONSON: Diane Aronson. Yes, all three viruses. But I have a particular note of the PCV 2 as it's a new virus.

DR. HAVENS: Peter Havens. Yes, but I would do this for all three viruses not as a test of infectivity but, rather, to quantify the virus in the preparation using the principle that people have the right to know what they are taking and even inert ingredients in capsules are quantified. So this would be part of identifying the purity of the drug in one way or another in the same way that you quantify the amount of glucose in another capsule.

DR. GLESBY: Marshall Glesgy. No.

DR. McGOWAN: Ian McGowan. No.

DR. CLAY: Patrick Clay. No.

DR. LUQUE: Amneris Luque. No, but I remain very concerned about surveillance and I think it is something that should be kept a close tally of for the future.

MR. BURKE: John Burke. Yes, all three.

DR. KERCSMAR: Carolyn Kercsmar. No.

CAPT CHAPMAN: Louisa Chapman. No.

DR. HENEINE: Walid Heneine. Yes for all three until at least the question is settled by looking at transmissibility of these viruses to the patients.

DR. THACKER: Eileen Thacker. No.

DR. ARMSTRONG: Greg Armstrong. No, unless there were some evidence that these viruses are being transmitted to humans or that the ecology of the viruses was changing in swine.

DR. ANDERSON: Larry Anderson. No.

DR. McGOWAN: Thank you very much.

Now we can go to Question 1, subsection c. The question here is: If testing is warranted, should the acceptance criteria for lot release allow for a limited number of infectious virus?

Really, the group--we can discuss this in a second, but I think the group who would vote on this would be the same individuals who said Yes, this is something we should do. I presume that is what we decided before. But, nevertheless, the whole committee obviously can discuss this issue.

I think what we are addressing here is lot release in terms of obviously moving the drug from the production facility into distribution, should there be some barriers set in terms of infectivity readout.

Would anyone like to begin that discussion?

DR. PARRISH: I would advocate that the main reason I said Yes is that I think, like someone else commented, it is important to know what is in the product.

I would not be specifically concerned about having a small amount of residual virus. I think that it would be important to know what was going on, and I think the issue of serology and testing in recipients and in other people exposed to these viruses is something that probably needs to be monitored in concert with sort of this bit of ongoing effort to identify the pathogens and really understand more about the susceptibility of humans to these infections.

MS. ARONSON: Forgive my lay perspective on this, but what I am hearing about is the vaccination that takes place in the United States. But the product comes from Europe, as well. So, it seems like it may be more of a load in some batches than in others, and it seems that maybe sort of a standard of understanding could be learned of what a level is.

DR. McGOWAN: Thank you.

DR. CHERNICK: I might say in addition to this, is it possible that the batch, each batch be labeled where exactly it was made, introduced?

DR. McGOWAN: That has got a specific question. I don't know if the company feels comfortable and wants to share with that. I don't know actually if they blend pancreatic organs in different centers in Europe and the U.S. or you keep them separate or not, or if you want to even address that, I don't know.

DR. SANDS: We do have a process to obtain the appropriate enzyme concentration, so it does involve a blending process.

DR. McGOWAN: Right, but does the product from Europe, is it co-mingled with product from the U.S.?

DR. SANDS: All is manufactured in one location.

DR. McGOWAN: Okay.

DR. PARRISH: Personally, I would say that it would be interesting to know that. But I think it would be better to come up with a common standard that worked for all possible geographic origins rather than, you know, if pancreas comes from one region or another. I think it is going to be very difficult to come up with a common set of standards that can be applied across the board, and also presumably, some of these standards may also apply to other manufacturers' products in the future, which we really have no way of understanding at this point.

DR. McGOWAN: Thanks. Dr. Chapman had a comment, question?

CAPT CHAPMAN: Well, I have a comment on the question. 1c in front of us asked us if testing is warranted, should there be an acceptance criteria for lot release that would still allow a limited number of infectious viruses in the lot.

I realize we haven't voted on this yet, but for myself, given that we know these viruses are ubiquitous, and we know that this product is essential, then, obviously, the

answer has to be Yes, if you are going to test, you are going to have to release the lot and have some acceptable level.

The second question is if Yes, is there a viral load below which cross species infectivity is less likely to occur, and my response to that is I have heard no data in this session that would inform that question.

So, if there is data that informs that question, it would seem to me we need to have it brought to the table before we can say anything intelligent about it, or at least I need it brought to the table.

DR. McGOWAN: Dr. Havens.

DR. HAVENS: Well, I would argue that the only answer here from my perspective is no. Even though I think testing is warranted, I wanted to know that so I knew what was in the drug.

But there is no way to show infectious virus to humans, because it is not. So, this is an issue of what is in the drug but shouldn't delay release, and you wouldn't know what number to set this at and how would you measure infectiousness, what Dr. Glesby was talking about this morning essentially.

DR. McGOWAN: I mean, to be practical, the scenario we are looking at is having a 2-ton batch of product, which will probably have molecular evidence of one or more of these viruses.

DR. HAVENS: Right.

DR. McGOWAN: And we don't have a correlative infection in humans so I am not sure how we are going to work out what level of infectivity if those assays are even available would have meaning in terms of theoretical risk.

So, we are operating in a data-free zone to some extent. Where do you set the bar and why?

DR. HAVENS: Exactly right.

DR. CHERNEY: In the past, FDA has realized that sometimes you don't have the data. But what we base it on then is process capability, what is the process historically delivering to patients.

In this case, we have lots of lots and lots of information about what the average lot looks like, and so you set standards to make sure that the material that is being released is representative of the product that has been released before, and not a whole different level of viruses being contained in that.

So, there is some basis to make a decision, it is not rigorous and it is not based with a lot of data.

DR. ROSENBERG: And to add to that, the experience that we have had to date with the manufacturing process that produces lots of a given nature, we have, in essence, a safety database even though we all acknowledge that the investigations into whether patients have truly been infected or not have been limited.

Nonetheless, we know that there have been, at least in recent times, no pandemics that have arisen from this, so that, you know, we can correlate at least roughly a patient safety database with a given viral load or an average viral load in the product.

DR. McGOWAN: Dr. Anderson, I think was first, and then Dr. Heneine.

DR. ANDERSON: The question in (d) is, is there a correlation between viral load and the risk of cross species transmission. The answer to that is clearly Yes. However, it may be from incredibly infinitesimally small, to still infinitesimally small, I mean if you are talking about 10^{30} probability of having a change.

So, I think increasing viral load does increase

just by probability that you might have a virus that would be able to infect and cause disease in humans. That still may be incredibly unlikely, and I think we are not going to know what that number is.

So, I think if you are going to screen, look at infectivity, what you are going to end up doing is what is practical. You know, what percentage of lots are you willing to give up to get some little added level of safety? I suspect that's the way this works.

I think the other part of that is understanding what the cost of doing the screening and selecting out lots is, in the manufacturing process, and then to the cost of the product.

I have no idea about that. If you make five lots in a year that meets the need, adding some viral screening probably isn't going to add much cost to the product. As you go up on the number of lots, then, the cost of the screening becomes maybe an important contributor to the cost of the product.

We haven't talked about that and maybe that's not relevant. But that does come into play.

DR. McGOWAN: Well, you could model all these

things, but I mean the obvious point is no, that's not where the expense is. Expense is a company losing a lot, a 2-ton lot of product. For some, it would appear a somewhat arbitrary boundary we are going to set, which you yourself suggested might be more utilitarian than scientific.

DR. ANDERSON: I figure it has to be, because we do not know what the probability is. At this point in time, if you do screening and you find presence of antibody in the patients that suggested their infection, then, that changes the picture maybe a little bit. And then if you see if there is disease, that may change it more.

DR. McGOWAN: Walid.

DR. HENEINE: Yes. I wonder whether there are data to address the in vivo infectivity of this product and its susceptible host like the pigs. Do we know whether these products, if given to susceptible pigs, do transmit these viruses or not.

What is the risk of transmissibility at least in the worst case scenario, which is really the susceptible natural host for these viruses. Have these studies been done or at least can this be inferred from the level of infectious titers that we have the product?

DR. McGOWAN: Well, the specific experiments, such as you describe, the company could tell us or not. But I think our experts could tell us or speculate perhaps about whether that might be the case.

DR. PARRISH: Unfortunately, I don't think that would be--I mean it could be done, I am sure. There is probably a correlation between infectivity for tissue culture cells and infectivity for the natural host animal. Unfortunately, I don't think that is going to tell us anything about relative risk for humans.

I mean my feeling about this in terms of voting yes for the original question, one was that, you know, it is more getting perspective information than necessarily being able to make a judgment based on what we already have, what we already know about it.

If there was one batch that had a million fold more of one particular virus in an infectious form, then, I think that would be useful information to have. If, in fact, the levels, when they exist at all are very, very low, then, I think that would allow us to retrospectively look at previous batches where the information is known and have some sort of evaluation of their relative risk from

infinitesimal to slightly more than infinitesimal, as Larry would say.

DR. THACKER: One other point when you talk about this is you are looking at two different things, too, especially with porcine circovirus. There is infection and then there is disease, and then you can give with this virus, especially low levels cause no disease. So I mean what are we going to measure? Yes, it sees a virus. A lot of viruses, and Colin can probably speak better than this, but I know, like with some of the viruses we work with, two virions can cause infection. But what does it mean?

So, my question with this is as we look at testing all of this stuff, to do it for preliminary data is one thing, to put this as a standard forever, is that what we are doing?

DR. McGOWAN: Dr. Glesby.

DR. GLESBY: I guess several people have recently raised the issue of sort of gathering this information on the amount of virus in the product, sort of for future epidemiological investigations.

I guess I am just questioning that whole principle I guess, given that it sounds like your average person,

let's say, with cystic fibrosis or other pancreatic disorders will likely have taken multiple different products over the course of their lifetime as well as given the amount that they actually have to take of a given product.

Clearly, a multitude of lots, I am not sure that anyone could ever design a study--and maybe we will have an opportunity to talk about this later--that would really be able to pin things down to a specific lot, exposure to a specific lot.

DR. McGOWAN: Dr. Chapman.

CAPT CHAPMAN: So, here is the question that occurs to me. If the reason for if you vote to test lots, to quantify virus and then test for whether that virus is infective, and the reason for doing that is to be able to correlate it with disease in the future, would it be more cost effective to simply freeze a number of aliquots from each batch and then have them available to use as part of postmarketing surveillance if you seem to be seeing a cluster of unusual levels of distress in patients who have received a common lot.

DR. McGOWAN: I think there are lots of things we could do like that or make suggestions to FDA those kind of

things in the sense of almost pharmacovigilance, not that that is reasonable.

I think it might be time to move towards the vote. The vote in this instance is restricted to really those six individuals who thought it was a good idea to do this. So, for those of us who didn't, we should stand back on this.

For those six people, you are really being asked here that if testing is warranted, should the acceptance criteria for lot release allow for a limited number of infectious virus. You can either vote Yes, No, or Abstain.

If you could vote now, please.

MR. BURKE: Excuse me. Let me ask a clarification question. So, if we vote No on this, then, the lot is just released and, if you vote Yes on it, then, you are going to establish a threshold for release.

[Electronic voting]

DR. McGOWAN: Just to read into the record then for Question 1c, we have: 4 said Yes, and 2 said No, and there were no abstentions.

Could I just ask, then, for administrative purposes, those people who voted, could you give your name and your vote, please.

DR. PARRISH: Colin Parrish. Yes.

DR. HAVENS: Peter Havens. No.

DR. CHERNICK: Milica Chernick. Yes.

MS. ARONSON: Diane Aronson. Yes.

MR. BURKE: John Burke. No.

DR. HENEINE: Walid Heneine. Yes.

DR. McGOWAN: Okay, great. Thank you.

Now we can go to--it is actually not a question, it's an opportunity for further discussion, which I think will be more contentious, that the committee can contribute.

Essentially, if Yes, is there a viral load below which cross species infectivity is less likely to occur?

I think Dr. Anderson from CDC has already alluded to the fact that more is more likely to transmit the parameters of increased risk they were somewhat uncertain.

Would anyone else like to comment, or Dr. Anderson, about this concept of can we set a viral load?

DR. ARMSTRONG: Actually, I didn't want to comment on that, but on Question (c) I am not--you could answer, you could mean the same thing and answer Yes or No.

For example, Dr. Havens, did you mean that lots should not really be released even if there was infectivity

present, or did you mean that lots should be released independent of any infectivity, because I mean I think--your prior comments, I would guess you meant release it independent of infectivity.

DR. HAVENS: Well, my prior comments actually were that the question was badly phrased because you already identified you can't identify human infectivity since there is none.

So, you can't hold or release based on human infectivity. Therefore, the number that you get, I am interested to know in the same way that I am interested to know the grams of protein or something. But I would not hold up any lot based on that. I would release it independent of the information. So, you are exactly right, good question.

DR. ARMSTRONG: Colin, your answer Yes, did that mean that you should release its infectivity or not?

DR. PARRISH: I was looking at Question 1, which is--so I would actually release it with some infectivity. But I think the issue we are talking about now is whether or not there is a level at which we would set the bar.

DR. HAVENS: So, your answer to Larry's question

is yes, there is some level at which you might consider holding back a lot. You meant yes in that context.

DR. PARRISH: Yes, that's correct.

DR. HAVENS: And I meant no, there is no level at which I would suggest holding back a lot. I would release it no matter what you found.

DR. McGOWAN: I hope that's clear to everyone.

[Laughter.]

DR. HAVENS: That's why it's a good discussion.

DR. McGOWAN: Is that the end of the discussion? Would anyone like to discuss the concept of viral load?

I think we need to try and summarize that a little bit so we have got clarity as we move forward.

My sense is that a group decided that yes, indeed, they would like to have batches tested for these viruses. And then all of those, a subgroup, also felt it would be a reasonable idea to define some level of infectivity, which would have consequences in terms of whether a batch is released or not.

Others thought that was not a good idea. They might want the data but they wouldn't use that as a parameter to withhold moving the product into distribution.

Does that address, reflect our sentiments? Good.

Let's go to Question 1e. Are there any other viruses of concern that have not thus far shown zoonotic potential but should be tested on a routine basis?

That is a question I think for everyone on the committee, and would anyone like to start the discussion in terms of other viruses? I know Dr. Heneine before was talking about porcine endogenous retroviruses, if he wants to talk to that, or if there are other viruses de jure we should talk about.

DR. HENEINE: Thank you for putting me on the spot. I think the point with the PERV, again as echoed by many of the speakers, the experience you have with the porcine factor VIII concentrate that had high levels of porcine endogenous retroviruses, as well as porcine parvoviruses, was a case in point that may be relevant to this situation today.

There, the studies looked at the levels of these viruses in the products in several lots, and it was ubiquitous and it was high. There was some work on infectivity of that product at least for the PERV in Dr. Wilson's lab, and there was also an investigation of

transmissibility to patients who have used chronically those products for several years.

There, the data was negative for the patients. There was no evidence of seropositivity for both viruses. So, it was a model study investigation where the contamination was identified, was characterized, and transmissibility to patients was evaluated.

I think the frustration here is that part of these data are not available for the committee, so that we can-- that would inform our decisions on all these questions, and that was a little bit strange because the product has been around for a long time and the population size that has used this product frequently is enormous.

So, it was assuring from the sponsor to know that they are planning on doing those studies, and we would like them to elaborate further on the choice of viruses that they are planning on testing in the patient population.

But again at this point in time with this product, any evidence for safety, even though the risks of transmissibility is low, is welcome.

In looking at patient screening, I would advocate and suggest to look not only at non-enveloped viruses, but

also enveloped viruses that we know may be present in the product itself.

Another point to bring about for regarding retroviruses, that although chemical treatment might reduce or eliminate infectivity, if these particles, at least these viral cores, retain reverse transcriptase activity, retain intact intergrade activity and genomes, that you could probably expect to see some integration. And, therefore, there is a risk with these steps if they are repeated over a long period of time to get some site-specific mutagenesis or some sort of harm to the patient.

So, at least for some viruses, loss of infectivity may not mean all the time loss of harm or loss of concern with these viruses. So that is another point to keep in mind.

So, PERV, probably the risk is very low. We have learned from xenotransplantation and patient cohorts that were tested with live cells and tissues that the risk with those sorts of xenografts was traditionally low. But here, it would also help to see surveillance data from the patient population that would confirm the expected outcome that there is no evidence of transmissibility.

But it is probably--and I again would welcome input or feedback from the sponsor about what levels of at least virus levels are seen even if it is not infectious in the product with a marker virus like PERV, which is present and cannot be eliminated by pre-transplant screening. It is present in the tissues.

DR. McGOWAN: So, Walid, there are two questions really for the Solvay group.

One was do they monitor for PERV at all with the caveats that I think the processing stage--according to Dr. Parrish, the isopropanol and the heat would probably actually reduce it very significantly such that you may not see it at batch testing at the end or you might still be able to identify it, but it wouldn't be infectious.

Then, the other question was perhaps are they in a position to provide us more detail about the clinical surveillance program because in their slide presentation it was ambiguous as to what they might be looking for in terms of blood samples, and so forth.

DR. HENEINE: I think the manufacturing process will probably eliminate infectivity of these viruses, of the enveloped viruses. But it is nice to confirm that by

screening of the patient population to look at whether or not there is any evidence of infection.

There is, with retroviruses, as I mentioned, also a lingering point that, you know, what are you infecting, what do you have. Do you still have reverse transcriptase activity at all or not, and do you see some at least any evidence of reverse transcriptase activity?

The porcine factor VIII product, that presumably went through a manufacturing process probably not identical, were probably included at precipitation, and so forth. That is common knowledge for factor VIII.

There was evidence of reverse transcriptase activity in the product so, yes, I am advocating for expanded screening at this point in time when we do not have any data on transmissibility to patients, expanded screening of a number of these viruses.

DR. McGOWAN: So, maybe someone from Solvay could tell us or we could ask them if they are able to tell us what they might think of the components of the surveillance would be serologically.

DR. SANDS: Well, I can explain to you that the actual components of the surveillance plan are as I have

described in the presentation, one to be agreed upon by the stakeholders because we believe we might have a list. As is pretty apparent here in the group, there is a wide variety of opinions relative what is most appropriate, and we believe that an appropriate surveillance plan is not only what we think we need to be looking at but it also needs to serve the purpose of the patient population.

So, we would entertain the idea of having the stakeholders brought together and prepare the list of things and what is feasible.

DR. McGOWAN: Thank you. Dr. Chapman.

CAPT CHAPMAN: Since PERV has come up, I actually would like to present a counter argument to my retrovirologist colleague, but from a clinical perspective.

First of all, we are speaking about some studies that some people in the room may be very familiar with and others may not. So let me just back up and say PERV is an endogenous retrovirus that lives in the genome of every cell in every pig and can. under certain circumstances, activate from live virus that could maybe infect human cells.

When it has been studied in xenotransplantation, we have looked at patients who had all of their host

immune's protective barriers breached, had living pig cells with PERV in it place into their bodies and had, in some cases in the Parody, et al Science paper, which we are also co-authors on, documented microchimeric porcine cells in place for up to, what was it, 8 years, after initial exposure.

So, 8 years of opportunity for PERV to come out of the genome of those cells in place and infect the patients, and yet we could find no evidence of infection with PERV.

In addition, while it is referred to studies, where patients who got porcine factor VIII, hemolytic patients who got porcine factor VIII, again defenses breached, put directly into the bloodstream with documented porcine parvovirus and also presence of PERV in that product, and again no evidence of infection in those patients could be identified.

So, I would argue that we actually have some pretty good evidence that, with far more intimate exposure, we haven't been able to infect a human with PERV. In this case, clinically, you are taking a product that may contain PERV in the cells of pig cells.

You are transiently exposing it to people and

actually the alimentary canal is outside of the human body. So, it is passing through the alimentary canal. You would have to have a much more transient exposure measured in hours, and you would have to postulate that somehow that PERV could mobilize from the cells and infect, and I think actually it is hard to justify testing for PERV or raising the specter of retrovirus fears in this setting with this product.

So, I would vote against that.

DR. McGOWAN: I think our next person is Dr. Parrish but I can't resist, as a mucosal immunologist, saying, you know, the contention that the gut is outside the body is probably something that we could debate later in the day.

CAPT CHAPMAN: That's what I was told in anatomy class. What can I say?

DR. McGOWAN: I will pass it over to Dr. Parrish quickly.

DR. PARRISH: I just want to say that I think this, you know, assuming the factor VIII issue is an important one--but I think that, you know, personally I don't think that this is the same situation at all.

And I don't personally see, you know, the risk of eating a contaminated pork product or this particular drug is going to be all that different in the context of the exposure to it.

I do see that, you know, these patients have been exposed to large amounts and apparently, for the cystic fibrosis patient, it could be for the entirety of their life starting when they are a newborn. So I think that there are, you know--it's not just like eating a pork chop but, you know, we should be considering sort of the additional risk of the sort of long-term sustained exposure that might occur.

DR. McGOWAN: Dr. Rosenberg.

DR. ROSENBERG: Yes, I was actually going to echo Dr. Parrish's statements in that, you know, the level that the cell burden in the xenotransplants, I am not sure how much was left over a period of eight years to provide a nidus for that kind of infection and also that, you know, putting something in IV, which is not the natural transmissibility route, actually may--even though it bypasses the gut, the gut is the natural route of infection.

So, I would actually be somewhat more concerned about products that are going in orally than products that are just shot in intravenously that may not find the receptors that they need for infectivity.

CAPT CHAPMAN: It is the natural route of infection for parvovirus but not for porcine endogenous--

DR. ROSENBERG: Yes, I was mostly addressing the parvo issue.

DR. PARRISH: Actually, interestingly enough, the natural infectious route may well be in the oral pharynx and possibly an infection of the tonsils rather than actually an infection of the gut. I am not actually sure that this is the most susceptible route if it is, in fact, enteric coated.

DR. THACKER: Don't forget over long-term periods of time, if it was causing infection, if it never again, like Dr. Anderson said, caused disease, then, you would get immunity anyway. So actually taking it long term would potentially be--if it was always in the product, would probably not increase the chances of changing and it would actually potentially decrease those chances because pigs become immune to these viruses over time.

These are not viruses that prevent immunity.

DR. McGOWAN: I am going to take one more question and comment, and then move towards the vote.

Dr. Havens.

DR. HAVENS: Well, we have been mixing questions of testing people versus testing the product, and I am just trying to get some clarification. This is testing the product and then the discussion has been solely about PERV. But you referred to that as a marker virus, and so there might be other marker viruses of interest. So, we are talking about testing the product.

DR. McGOWAN: My understanding, unless FDA differs, we are talking about testing product for other viruses.

DR. CHERNEY: Correct.

DR. McGOWAN: Dr. Anderson.

DR. ANDERSON: I think this discussion illustrates the difficulty in the sense that when you get a positive, what do you do with it. In the context of that, there are tools available to look very broadly and probably relatively efficiently and, from a scientific perspective, I would love to do it. From a product screening and making decisions

about whether or not to release or use a product, I am not sure I want to go there.

My guess is that if you screen, you are going to find some additional viruses. I would be kind of surprised if you didn't. I mean 30 viruses in a species maybe sounds like a lot but it really isn't and, in some ways, I think it is not so much a point to think about in this particular meeting for this product. But a longer term issue which I think is part of what you are thinking about, how do you approach these kinds of products.

I think it merits additional discussion with a wider group of people that maybe isn't quite sufficient time to come to the conclusion at this point in time, what in the future this should be done, should it be a research public health product versus a company? I mean a question.

I mean there are a lot of issues here.

DR. McGOWAN: I think we can probably move towards voting. I mean just to reiterate again. This is about really should we be testing for viruses in the product. I think the caveat that underlines most of these questions is in the context of product development.

I think there are some really interesting

scientific questions we could postulate or ask, but this is really I think in terms of helping FDA and to help the company. So, in that light, then, perhaps I can ask everyone to vote either Yes, No, or Abstain, bearing in mind that if you vote Yes, as we go around the room, I will ask you to provide us with your preferred virus.

So, if you are ready to vote, we will do that now.

[Electronic voting]

DR. McGOWAN: In response to Question 1e, we have 3 people voting Yes, 11 voting No, and we have 2 abstentions. So, if once again we can go around the room starting with Dr. Ferry, give your vote. If you voted Yes, then, briefly, let us know if you can what virus you would like us to look for.

DR. FERRY: George Ferry. No.

DR. PARRISH: Colin Parrish. No.

DR. CHERNICK: Milica Chernick. Abstain.

MS. ARONSON: Diane Aronson. Abstain.

DR. HAVENS: Peter Havens. Yes, and I would ask Larry Anderson and the virologists in the group to work with the FDA and the company to decide what the most appropriate marker viruses would be.

DR. GLESBY: Marshall Glesby. No.

DR. McGOWAN: Ian McGowan. No.

DR. CLAY: Patrick Clay. Yes, and along with the comments just made, which probably also goes to Questions 2, 3, and 4, which is to identify on a periodic basis in conjunction with the interested parties what viruses may need to be further tested for.

DR. LUQUE: Amneris Luque. Yes, and I will defer to the experts to decide what is best suited for testing.

MR. BURKE: John Burke. No.

DR. KERCSMAR: Carolyn Kercsmar. No.

CAPT CHAPMAN: Louisa Chapman. I interpreted on a routine basis to be a key phrase here and said No. There may be clinical epidemiologic events that raise a question of specific tests in the future should be addressed.

DR. HENEINE: Walid Heneine. No.

DR. THACKER: Eileen Thacker. No.

DR. ARMSTRONG: Greg Armstrong. No.

DR. ANDERSON: Larry Anderson. No.

DR. McGOWAN: Thanks very much.

I have an unscheduled question. Would people like to have a 10-minute break, or would they like us to

continue? I will address it to the Committee. I think you should all vote.

I will take that as we probably all do need a 10-minute break. So let's do that. Please stick to 10 minutes, otherwise, we will be here late. Thanks.

[Break.]

DR. McGOWAN: We are going to restart the meeting.

We are going to move now to Question 2. I would like, if possible, for the Committee to sort of try and focus on the specifics contained within some of these questions.

Question 2 states that to control the risk from unidentified emerging viruses, Solvay has proposed a number of options for animal disease surveillance programs and continued risk assessment evaluations for source animals. Should a detailed plan for these programs be required?

Before I open it up for discussion, just the question here focuses on animal disease surveillance and risk evaluation, risk assessment for source animals. So, if we can focus on that area, and are there any comments or questions from the panel.

DR. PARRISH: You mean in addition to the ones

that they have proposed? I am not quite sure what the question is asking.

DR. McGOWAN: Could someone from the FDA clarify for us the intent?

DR. ROSENBERG: At the time we wrote this question, we had not received the specific plan that has subsequently been identified. We haven't really had a chance to go over that.

This was intended to be a more general question asking for a detailed plan, which obviously, the company is considering providing.

DR. McGOWAN: In that context, would you like us to sort of discuss, critique what has been suggested?

DR. CLAY: The plan they provided is for their product, not for animal surveillance.

DR. McGOWAN: That is what I was going to come to. I couldn't remember any details on animal surveillance per se, but certainly details on human surveillance. But did we miss something?

DR. ROSENBERG: No, I don't think we have. Our understanding was there is a detailed plan for animal surveillance, as well as patient surveillance. So, your

comments would be welcome on that.

DR. McGOWAN: Dr. Chapman.

CAPT CHAPMAN: In the presentation in this open session, the statements were made about collecting product only from Europe and the U.S. where there were animal, disease control, policies and effect, and public health and herd surveillance, and so on.

This morning, and I think I can refer to this, because it occurred in the closed session--but it is not related to any proprietary information--but I asked a series of questions to try to define in my own mind what that meant.

As I understand what that means is in the U.S., and in Europe, when pigs go to slaughter for food, they are visually inspected and allowed to go forward only if there is no visible evidence of disease on visual inspection, and if they have come from a herd where there has been no evidence of an outbreak that reached a level of concern that brought public health intervention.

I think it would be reasonable to request that at least that level of specificity and clarity be included in not just we collect from these countries for this reason,

but what does that translate into in terms of actual product safety.

DR. McGOWAN: Thanks.

Dr. Parrish.

DR. PARRISH: I was actually referring to the stuff that was in the open session on page--I am not quite sure what the page is--on page 6, it is called "ongoing virological surveillance," literature searches, subscription to Pro Med, networking with experts--I am just paraphrasing, regular sequence alignments by blast, I am not exactly sure what that involves.

I think the question is, in the context of the question, you know, do we want--I mean do you mean this kind of plan, or are we asking about an additional plan? Or do we just want to not give, you know, say that a plan is a good idea, but not specify exactly what it would involve?

DR. McGOWAN: We looked at the suggestions about, whether be it in the backgrounder or in the actual presentations. But I haven't seen a specific plan which addresses from the farm to the factory. I mean there are elements laid out but there doesn't seem to be anything extraordinary.

I think you lay out that use,porcine-only slaughterhouses that are regulated by the European Union authorities or the USDA, and so on, and so forth. But I didn't see any more than that so there is no extra vigilance in terms of testing animals other than by visual inspection.

So, I don't know if the intent of the question was should there be an increase in surveillance beyond what is being laid out here or not.

DR. CHERNEY: I think if you look at the ongoing virological surveillance plan, you see they talk about follow-up trends in food industry. But what does that mean, and what are the details of that? How are you going to do that--you know, more granularity to the actual plans because there is a general proposal--and we just saw this when we got the briefing documents. So the expectation is what are the specific details; should we have a plan, and then if we do, what kind of details would we get.

DR. McGOWAN: One option is that we would say yes, there should, of course, be a plan, and there needs to be more detail provided, touching on these elements that have been painted in broad-brush strokes, but that's all.

DR. CHERNEY: If you think that these elements are

something that should be incorporated in the plan, and if you can think of other elements that might be incorporated, that would be fine.

DR. McGOWAN: Dr. Anderson.

DR. ANDERSON: Specificity makes sense. But I think we probably need to be a little careful in what that means in terms of requiring them to do.

Any surveillance beyond, you know, I mean that is, in a sense, other people's responsibility, and I think it is probably a little much to ask, I mean in terms of individual herds and things like that, that may be a bit much to ask a company that is making one product associated with swine to take on that kind of responsibility.

I don't know what the intent here is.

DR. THACKER: I can tell you this, that probably if they started asking all of the different swine producers the health status of their farm, they would get laughed off the--and then also, the other thing that you would have to recognize is that with it being from the EU and the U.S., health status is not a static thing but is constantly changing at every given moment.

It is going to be critical for a product like

this, and this is going to be something that the FDA will need to -- should probably work with somebody like the OIE and APHIS. They refer to talking to them, and they are aware of that.

I mean the bottom line is, is there is no way that any of us can look in a crystal ball today and say these are what exactly you need to look for other than what we have talked about today.

I mean, and then it could change tomorrow. I mean somebody over in Europe could have a classical swine fever outbreak. That is going to shut down a lot of the things anyway, because those things are constantly being surveilled for.

It is going to be really hard and what needs to be set up for something like this is a plan, how often they would talk to whoever of the regulatory agencies. It has got to go through the regulatory agencies that are constantly doing surveillance.

If a new disease breaks out, and in my lifetime I remember the parvo in dogs and the feline viruses and the porcine viruses, and things like that unfortunately, and I mean these things happen, and with a product like this, they

are going to have to have a mechanism to take that into account.

We can't tell you today. That's my thoughts on the whole situation. I don't know what Colin's thoughts are.

DR. McGOWAN: Dr. Clay.

DR. CLAY: On the animal surveillance aspect and whether or not we recommend a plan, and what is included in that plan, is it within our ability to comment any on the duration of time or the amount of product that should be available to the company in order to continually supply the drug while the outbreak is identified, should there be an interruption of supply of product. Should they need to have like a 12-week supply of this ahead of time? I don't know.

DR. PARRISH: Since my name was brought up, to try to address this, looking at the question itself, which is unknown emerging viruses, I mean that is clearly not within the purview of a company such as this. It is more of a general concern for the swine industry and it is more of a general concern for the pharmaceutical industry and presumably the food industry, as well, that is raising pigs for food.

So, I think that the sort of thing that they propose is, you know, if it was given more details, would probably be a reasonable proposal. I am not talking about it specifically because I haven't really had a chance to read and think about it.

Given that the question has two parts, one is should there be a plan, I think my guess would be that probably a plan is a good idea. The second is what should be in the plan, and that is a much harder question to answer.

DR. McGOWAN: I am not sure we fully responded to Dr. Clay, but I think what you are talking about is going a little bit off of topic in a sense, those contingency plans, if there was a disruption in the supply chain, is that what you were asking about?

DR. CLAY: Right, because it's animal disease surveillance programs. So how does their company work with either existing programs or the development of future programs so that they are assured of supply for the drug.

DR. McGOWAN: Some of that could be an element of the plan they put together I guess.

I think we can vote on this now. I think it is

relatively straightforward. So I think everyones has had a chance to read the question: Should a detailed plan for animal surveillance programs be required?

If people could vote Yes or No, that would be great, or, of course, abstain.

[Electronic voting]

DR. McGOWAN: In response to Question 2a, 15 people voted Yes, 1 voted No, and there were not abstentions.

So, if we could go around the room starting with Dr. Ferry, and those of you who said Yes, there should be a program, I will let you say what you think the elements should be, or you could probably make a fairly abbreviated comment.

Dr. Ferry.

DR. FERRY: I voted Yes, but there is a general outline there. I think it's premature to try to refine that too much further. But, at some point as we go forward, the company is going to have to outline a little bit more detail, and I don't have any specifics I would add to that.

DR. PARRISH: I would say basically the same thing. It is sort of like the Rumsfeldian thing, you know,

the unknowns are very hard to predict. But I think it is good to have a contingency plan in there.

DR. McGOWAN: Once again, just name and vote. That was Dr. Parrish saying Yes.

DR. CHERNICK: Milica Chernick. I will add to whatever slide was this continuous development and update of analytical methods, whatever that means.

MS. ARONSON: Diane Aronson. I voted Yes and I will abstain from discussion.

DR. HAVENS: Peter Havens. Yes.

DR. GLESBY: Marshall Glesby. Yes. Nothing to add.

DR. McGOWAN: Ian McGowan. Yes. I agree with the previous speakers.

DR. CLAY: Patrick Clay. Yes.

DR. LUQUE: Amneris Luque. Yes.

MR. BURKE: John Burke. Yes. As a previous federal regulator, I think SOPs, or standard operating procedures, are a good idea.

DR. KERCSMAR: Carolyn Kercsmar. Yes.

CAPT CHAPMAN: Louisa Chapman. Yes.

DR. HENEINE: Walid Heneine. No. I think what

they presented was reasonable.

DR. THACKER: Eileen Thacker. Yes, and what everyone else said, it has to be just developed in more detail.

DR. ARMSTRONG: Greg Armstrong. For this question, the devil is in the word "detail." But I think that they need to develop some sort of standard operating procedure and it should include in it some specifications for when and how they will notify FDA, if they pick up some sort of a signal from the herds from which they are receiving the product.

DR. ANDERSON: Larry Anderson. Yes. I think that really building on existing surveillance system, and it is not to ask them to introduce a new surveillance system, because I think that is too much.

DR. McGOWAN: Thanks very much.

We didn't really touch on the use of indicator cell lines and animal testing. My colleagues in FDA, I think that could be engrafted into the discussions which need to go on around what the components of the plan will be. Do you want us to go into that more now?

It is really about using I guess indicator cell

lines, animals. This is 2b.

DR. CHERNEY: I think the question was you can have these general viral tests and they generally aren't employed, nor are there any utility in employing something like that to look for emerging viruses that you might not detect.

DR. McGOWAN: Great. Let's move on to Question 3 which again may be historical now, I suppose, because it addresses the issue of evaluation, risk identification in patients. I think Solvay did present us with outline proposals today.

But the question is: Solvay has not formally submitted a plan for continued viral risk identification and evaluation in patients taking Creon in the postmarketing setting. Should such a plan be provided?

Maybe we can discuss that briefly and then move towards a vote contingent upon the fact that they have presented some outline guidance today.

Would anyone like to comment on this aspect of the development plan? Dr. Chapman.

CAPT CHAPMAN: Correct me if I am wrong. I think what we heard presented were plans for retrospectively and

prospectively looking for clinical indicators in disease, is that correct? But I don't think I heard a plan for retrospectively doing case control studies or something to look for serologic evidence of past infection prevalent at a rate in people exposed to the product that is discrepant from man, and people who have not been exposed.

We heard that FDA was going to do that and I guess I don't really care who does it. But I think it is important and kind of basic first step, you know, even if you expect a negative study, and all it does is support regulatory policies and allied concerns.

DR. McGOWAN: Identify the retrospective phase and a prospective phase, and retrospective is using a U.S. claims database and the United Kingdom GP database to look at probably disproportionate incidence of diseases related to use of these products, and then moving prospectively, I think it was still in the phase of negotiation with stakeholders but would imply a level of surveillance including serosurveillance and, given that that would be then in the portmarketing setting, it seems to address the question.

Marshall.

DR. GLESBY: I guess with regard to the retrospective studies, for example, I am having a hard time understanding like what the control populations might be because, obviously, we are dealing with people with a lot of underlying morbidities and how could you ever see a signal, who would the controls be in these proposed studies.

CAPT CHAPMAN: Well, if what you are looking for is infection that these patients have gotten from this product, then, to my mind, control would be, I don't know, unaffected siblings who don't take the product who are within a comparable age range, because you would be looking for serologic evidence of past infection that was present in those exposed to the product at a disproportionate prevalence to what was present in people not exposed to the product

DR. GLESBY: Sorry, I guess I wasn't clear. I was referring really more to the clinical events rather than serological studies.

DR. PARRISH: I think there are clearly two parts to the issue. One is, you know, this issue of retrospective--and I have the same concern you do. I mean is there going to be--you know, if this is implemented, is

there going to be a population of cystic fibrosis patients who are not taking a product, either this product or one like it, and I guess the answer is probably not.

So, I think it is going to be very hard to work out what the clinical--and people with pancreatitis are probably similar.

There is also I guess the issue of, you know, people who take the product may be taking product from different sources, and so I guess that is another question is how much can you tie a particular disease or incident back to the particular product. Maybe that will become easier to sort out once it becomes on prescription and under better control.

The other issue is sort of serosurveys and direct indicators of an infection by one of the pathogens or viruses that we are concerned about here, and I think that is going to be probably easier to sort out at least in terms of what goes on in the future.

DR. HENEINE: Not much to add. I think many of us on the committee have echoed the same thing about the need for looking at the patient population, and determining the rate of infections or the prevalence of these infections.

I think, and as I mentioned earlier, we are glad to see at least the sponsor presenting some plans about looking about the prevalence of these infections in the patient population.

The next step would then be which viruses, and that can be discussed, you know, what is the higher priority virus versus lower priority virus.

DR. McGOWAN: Dr. Anderson.

DR. ANDERSON: I congratulate them for taking on the possibility of looking for clinical illness that might be associated with administration of this product but recognize that as others have commented, sorting out signal to noise is going to be exceedingly difficult because you are almost certainly going to have a higher rate of illness in this population for other reasons.

I think you maybe have a chance to come up with some illness that otherwise you would not have expected, and then it will be a hypothesis that would require further study to see if it's a problem.

I think the other thing is to remember that this product or a series of products have been available for a long time, and they have been safe as far as we can tell,

and I think any serious illness probably would have been picked up, any serious life-threatening event that was actually associated with this product.

I think there is a reasonable chance that it would have been. There certainly could have been illnesses that have been mixed. But I think there is a long safety record here, a presumed safety record that I think it makes it easier to think a little about what things maybe we don't have to do.

DR. McGOWAN: Dr. Clay.

DR. CLAY: The things you talk about in the prospective aspect, and specifically talking to Solvay here is setting up sentinel sights to collect biomaterial. But you don't mention any of that retrospectively.

Granted, as has been stated before, they have taken product from different manufacturers in the past. But would that at least give you some sort of a baseline that going forward you would be able to compare to, to see whether or not there are changes indeed occurring, also understanding that there are no specific antibodies for some of this.

But you propose perhaps storing blood samples or

biomaterial for the future. So I would like you to comment on why you would not look at that retrospectively or even on those individuals that you may be able to identify had just taken your product.

DR. SANDS: Let me first comment on the availability of the biomaterial in the retrospective analysis. The two databases that we are talking about, one of them is a claims-made database, the MarketScan, so that one is a little bit more difficult. That is just to help us attempt to scale a prospective study, and that is one of the things that we need to be able to do at the moment. You know, is it 50 patients, is it 500 patients, is it 1,000 patients, is it every patient. We don't know.

So we really need to be able to scale it, and that's one of the reasons we are looking at two separate databases.

Now, the GPRD database is an extremely different database. It does give us some accessibility to ask further questions. But once again it doesn't have biomaterials stored. So we are kind of at a loss when we look at a retrospective analysis.

But that is why we propose the prospective

analysis, to draw baseline levels with an understanding of what has been the exposure up until that point in time and then continue to monitor as we move forward.

DR. CLAY: So, then, you would consider identifying those individuals by a variety of methods who may have taken this product in the past and requesting that they provide materials for you to assess what may be there for previous exposure?

DR. SANDS: Great suggestion and we could continue to add that. Probably the GPRD database would be the best one to work with at the moment, or possibly working through the CF registry. But once again we would want to be able to identify patients then who at least if we are looking at our product, who have only taken our product, which is the challenge.

DR. McGOWAN: Dr. Thacker.

DR. THACKER: Well, that was the main thing I was going to say is because, from the FDA's perspective, if they have seen all these differences in the product historically, as far as activity, I mean the processing and the quality control for viruses, and everything else is going to be all over the boards. So while yes, it could tell you human

exposure to parvovirus or circovirus, or whatever PERVs or whatever viruses you want, it may not answer the question about Solvay's particular processing product now.

So, you would have to take that data that was collected from all these people over all this time and all these products with very great care as far as interpretation other than the potential of looking at transmission between pig, viruses and humans, because you would have no idea what the other companies did to try and even deal with viruses.

DR. McGOWAN: Dr. Havens.

DR. HAVENS: I would hate to see a negative study done on clinical signals stand as proof that these were safe. I hope that the company and the FDA are clear that we think that--that I think anyway, I can't speak for everybody else--that serosurveys are a critical part of any ongoing study to show safety since the clinical signals are inadequate.

So, the two large database studies might help you, but I don't think so. And you might want to discuss with the FDA whether or not you are better off putting your money into serosurveys alone to look forward at what you are doing.

DR. McGOWAN: Dr. Parrish.

DR. PARRISH: Just one comment. I think just to be specific, we are probably, you know, given the 70-year history of these products, looking for these rare events, you know, the unknown and knowns. So I think that, you know, we basically don't have the information about retrospective infection rates of a lot of people apart from a couple of references that have been alluded to.

So, I think there is a very big dearth of information. You know, if someone told me that 80 percent of the people who had taken the product had very high titers against peak parvovirus indicating past infection, that would be a different. I would consider that quite differently than if someone told me that, you know, none of them had antibodies showing past infection against the peak parvovirus or the circovirus.

I think we just basically don't have the information and it would be good for someone in the future perhaps the FDA is going to do it for the community at large, you know, to get that information so we can evaluate the risks better.

DR. McGOWAN: I think we can probably move to

voting on this issue. The question really again is risk identification and evaluation in the postmarketing setting, should such a plan be provided or augmented.

So, if we could vote Yes, No, or Abstain.

[Electronic voting]

Question 3a, 16 people voted Yes, no one voted No, and no one abstained.

So, if we can go around the room beginning obviously with Dr. Ferry. Everyone is going to say Yes, but if you could say very briefly what elements you think should be in the plan. I think we have kind of got there already. There clearly needs to be some thought given to study design, et cetera. But if we could go around the table and see what committee members feel would be useful components.

DR. FERRY: George Ferry. I don't have any other additional comments on that.

DR. PARRISH: I think I have already covered it, but Colin Parrish, yes.

DR. CHERNICK: No comment.

DR. McGOWAN: But that was a Yes you voted, Milica?

DR. CHERNICK: Yes.

MS. ARONSON: Diane Aronson. Yes. No additional comment

DR. HAVENS: Peter Havens. Yes. No additional comments.

DR. GLESBY: Marshall Glesby. Yes. I guess I would just add that I think it is going to be really, as I mentioned earlier, and others have commented on, very difficult to sort out clinical events retrospectively, perhaps prospectively, correlating with serologic data might be helpful.

I think serologic data retrospectively without any clinical data to accompany will also be difficult to interpret.

DR. McGOWAN: Ian McGowan. I voted Yes. I think this is a really interesting issue, but I think it is one which crosses different stakeholders. I mean it is something that the NIH could issue an RFA on, it could be something in collaboration with the CF Foundation, the Pancreas Foundation.

I mean there are all sorts of people who get involved with the science side of it, because we are really in a data-free zone, and I think prospective studies are

probably going to provide more useful information than dredging databases.

DR. CLAY: Patrick Clay. Yes. No further comments.

DR. LUQUE: Amneris Luque. Yes. No further comment.

MR. BURKE: John Burke. Yes. No further comment.

DR. KERCSMAR: Carolyn Kercsmar. Yes, and I would agree with Drs. Glesby and McGowan. I think CF is a very heterogeneous disorder, and patients often develop a whole host of clinical signs and symptoms that we often ascribe to just their underlying disease, and I think this may be an opportunity for hypothesis generating and prospective studies looking for a possible other explanations for complications of CF.

CAPT CHAPMAN: Louisa Chapman. Yes. As others have expressed, I am actually very skeptical of whether resources put into trying to look retrospectively at clinical findings are going to be well justified.

What I would think would be valuable, that looks retrospectively is what we have already discussed and what it sounds like FDA is working on doing, which is an attempt

to see whether, as a population, people who have been exposed to this are serologically different in terms of their apparent past history of viral infection than matched populations who have not been exposed.

There may be some value in clinical symptom studies going forward, but I think they need to be correlated with lab testing, and I think that retrospective study may give you a basis upon which to decide how much it's worth investing in active surveillance going forward, which is going to be relatively costly as opposed to a more passive stance of investigation of unusual instances of disease.

DR. HENEINE: Walid Heneine. Yes, and I concur with Dr. Chapman.

DR. THACKER: Eileen Thacker. No further comments.

DR ARMSTRONG: Greg Armstrong. Yes, and let me just say I think the consensus here is that these viruses pose a very low risk for zoonotic transmission to humans. So what we are looking for, we think we are not going to be able to find and, under those sorts of circumstances, probably the most sensitive testing to be able to prove that

would be serologic testing.

DR. ANDERSON: Yes, and I think the serologic testing is likely to be of most benefit, and I agree with Ian that in a sense, this is a broader issue. It isn't specific to this product, and it might lend itself to more of a research NIH approach or some other more broader approach looking for transmission of porcine viruses to humans from a variety of products that may come into play here.

DR. McGOWAN: Thank you. I think that is Question 3 put to bed. So now we can move on to the final question, which is quite interesting and really addresses product labeling.

We are asked: Currently, no information regarding the risk from viral contamination is provided to physicians and patients in product labeling. Is there sufficient concern that such information should be provided?

I suppose the background to that is if this product obviously receives approval for marketing, there will have to be a package insert of some kind, what language, if any, vis-a-vis viral issues should be contained within that. So, quite contentious.

Who would like to begin the discussion? Dr. Havens, you must want to say something.

DR. HAVENS: Please let the record show I did not raise my hand. The balance here is that I think we feel like there is a very low potential risk to patients from the viruses going through the manufacturing process and in the final product But the specter of a virus-containing product, which we know works and has a long history of safety, now competing with a potential other product, it needs to have a way for people to feel comfortable taking that product.

We would hate to have people who depend on pancrelipase say I am not going to take what is available or cheaper that I can afford or whatever it is, because of this potential risk of virus.

So, a lot of what I have been thinking about today has been how can you put into the label something that says this is what we know and everything we know about it suggests that the risks are very low, and this is really a very safe product because we have done A, B, and C, which everybody has been talking about.

So, I would say Yes, that something needs to be

provided, because it has already been in the New York Times and this is about to be on the Internet, and the people in the CF Foundation are very sophisticated medical consumers. They are not going to be unaware of this issue, and we need to address it straight on in a way that says there are viruses in pigs, there is PCR that is positive, but there is no human infectivity that we have been able to identify.

This is a class problem, not a Solvay problem, and that we, the FDA, feel like it's safe given our current state of knowledge but we are looking at it further.

Thank you for that chance.

DR. McGOWAN: Very nicely done.

Dr. Thacker.

DR. THACKER: I have to laugh. I am a veterinarian, and you watch these ads on the TV and every single drug you ever hear, and Ms. Holt said the same thing, you know, they all have all those--as a matter of fact, if you listen to them, it's the next best thing to sliced bread. They say they are going to cure all our problems. Then they list this list of every single thing that could ever possibly happen.

So, I think you just have to be just realistic.

You tell them that there is a potential; there is little evidence at this time of cross species, but it's there. I mean, shoot, after listening to what they say on the TV, this can't be that much worse.

DR. FERRY: The other thing I was thinking about, looking at this--so if this product gets labeled with all this information about viruses and whatever other products out there have not come to that state, patients can look, well, this one has got viruses, these other don't say anything, maybe they are better and safer.

So, I don't know. Somehow in the language I guess you want to make it specific for this product, but the risks could apply to all of these things. And I think somehow that needs to get across so that it doesn't appear to patients that this product has a big problem and the others say nothing.

DR. McGOWAN: But I think the caveat to that is all these pancreatic drugs are going to have to become aligned, they are going to be licensed. So there may be a transitional phase or this is the first one out to the block, but it's a class effect.

Dr. Armstrong.

DR. ARMSTRONG: I think FDA doesn't have a choice. I think they have to put it into the label. First off, as Ms. Holt pointed out, people with chronic disease, those that are interested in reading the product labels are used to looking at long lists of contraindications and potential side effects.

So, this isn't going to be that new to them. I think you would have to be careful how it is presented. I think it does have to be presented that, you know, all such products can be expected to contain certain viruses in them. But if you were, for some reason, to decide not to include it in the label, then, I think it would definitely become an issue.

I think that would be a big mistake.

MS. ARONSON: From a consumer perspective, yes, the cat is out of the bag so it does need to be addressed. The FDA has put forward a suggested warning product source label, and I am just wondering about this last sentence. It's on page 17, that says, "However, no cases of transmission of illness associated with the use of porcine pancreatic extracts have been reported."

I just don't know if that means it hasn't

happened. I am not sure whether something like that should be included or more the extreme rare risk or something that could be developed and an explanation.

DR. McGOWAN: Dr. Chapman.

CAPT CHAPMAN: I have been looking at the same model the FDA presented actually in their talk, that you are looking at, which is in handout, page 17, slide 34, the last slide.

I think they have got a pretty good start here. But, if I were given free rein, I would wordsmith it in this direction. I would say that this product, like all similar products that are derived from unprocessed live porcine material, are likely to contain viruses.

Similar products have been taken for the equivalent of 5 million patient years without any evidence that this has resulted in human infection or human disease, and I would not repeat the risk of infection about 12 times in 3 sentences. I think stating that it is there and that its theoretical would be adequate.

But also noting the evidence that suggests despite this, this is a safe product, but also including the last statement, which is if clinical symptoms are observed that

are suspected to be possibly infection, that physicians should report it appropriately.

DR. McGOWAN: Dr. Parrish I think was first, then, Dr. Thacker.

DR. PARRISH: Again, this is a class issue, and it's not just about pigs when you get to this kind of definition. There is no reason to think that a product derived from, you know, bovine material or ovine, you know, sheep or any other production animal, chickens is going to be free of viruses either.

So, I am not quite sure how much to say about it, you know, are we going to put a label on the butcher shop when you go in the door, and say that, you know, you are going to be exposed to virus, if you go to your vet, you are going to be exposed to viruses, I mean it is basically--I read the label that was proposed, and I have no trouble figuring out.

Again, I think something has to be written. But again this is part of the environment that we live in and there is no reason to think that this is any different from our other exposures that we have to viruses than any other animal product that we come across.

I am not exactly sure how to put it except that, as Greg was saying, we probably have to--you know, something has to be there somewhere.

DR. McGOWAN: Dr. Thacker.

DR. THACKER: The only thing I was going to say is, unless we really know that every single batch has viruses, I think you could say it has the potential to have viruses in it because we really don't know--that it is likely but it has the potential to have viruses.

I think that until they provide evidence that it is in every batch, which as far as I know, we did not get that information, right? We haven't received that information at all. I think just potential works.

DR. McGOWAN: Dr. Havens.

DR. HAVENS: Could you please leave out parvovirus? There are way too many telephone calls about dog parvo; "My dog has parvovirus. are my kids going to get it." It is not so special, it is not the human parvovirus B19. Isn't that right?

DR. McGOWAN: I would second that.

DR. ANDERSON: Go ahead, Colin. The answer is it is not parvo B19.

DR. HAVENS: Thank you.

DR. ANDERSON: There is no evidence it infects humans.

DR. HAVENS: Good. Leave it out.

DR. McGOWAN: There seems to be general consensus. I mean I think we can probably vote on this and then if people want to comment further about language, we could do that, too.

The questions are front of you. With respect to product labeling, is there sufficient concern that such information about viral contamination should be provided? Yes, No, or Abstain.

[Electronic voting]

DR. McGOWAN: So, for the record, Question 4, 16 people voted Yes, no one voted No, and no one abstained.

Again, we have to go around the room for the last time starting with Dr. Ferry and, if you feel so inclined, tell us what language and modifications you might consider for patients, providers, and so forth, the public.

DR. FERRY: Do you want to start at the other end and give me the last shot at it?

DR. McGOWAN: If you would like to do that, we can

do that.

[Laughter.]

DR. FERRY: That's all right.

DR. McGOWAN: Dr. Anderson.

DR. ANDERSON: Obviously, I voted Yes as everybody else did. I think the only thought I have in terms of what you say is it has to be honest and consistent with what you know, and you know that, because if you don't do that, you get in trouble. And I think that is only fair to the physician and the patient, and done in a way that's as least scary as possible. But it has to be honest.

DR. ARMSTRONG: Greg Armstrong. I have nothing to add.

DR. THACKER: Eileen Thacker. Voted Yes. I think that you don't have to differentiate the virus, because it may vary from batch to batch whether it is circovirus, parvovirus, whatever. Just be honest.

DR. HENEINE: Walid Heneine. Yes. Nothing to add.

CAPT CHAPMAN: Louisa Chapman. Yes, and I have already expressed my opinion.

DR. KERCSMAR: Carolyn Kercsmar. Yes. In over 20

years of taking care of CF patients, I don't think I have ever had a discussion with a patient about viral risk from their pancreatic enzymes but I am sure that the questions will start tomorrow.

But I would agree that the label should be honest, fair, and generic, and also that the label not be the only source of information for patients, and that the CF Foundation web sites will certainly be another vehicle to provide more in depth information for patients and that those things will certainly be updated over time.

MR. BURKE: John Burke. Yes, and no further comment.

DR. LUQUE: Amneris Luque. Yes. No further comments.

DR. CLAY: Patrick Clay. Yes, and would just like to see this written in a language that the patient would actually be able to understand, because there is no way this would make it to a consent form.

DR. McGOWAN: Ian McGowan. Yes. I agree with everything else that has been suggested.

DR. GLESBY: Marshall Glesby. Yes, and I am still in the middle, still nothing to add.

DR. HAVENS: Peter Havens. Yes. Very supportive of the CDC's recommendations to the FDA.

MS. ARONSON: Diane Aronson. Yes. What comes to mind is the two lines that you see on a menu about eating raw eggs or undercooked fish. I mean it is very simple, but it's a warning.

DR. CHERNICK: Milica Chernick. Yes, and no further comment.

DR. PARRISH: Colin Parrish. Yes. I think I have already had my say.

DR. FERRY: George Ferry. Yes. I don't really have anything else to add even though I am last. Thank you.

DR. McGOWAN: I am going to ask our colleagues from FDA if they have any final remarks or comments before I close the meeting.

DR. PARISER: Yes. On behalf of the FDA, we would really like to thank everybody for coming today. We have had people come from quite literally all over the country. We really do appreciate all the time and effort that you have put into this, and your comments especially have been very very helpful and we will take them very seriously as we move forward with these products.

Thank you very much.

DR. McGOWAN: With those comments, I would like to thank also all the Committee members for their help this afternoon and today, for the audience who have sat through all of this, and call the meeting to a close. Thank you.

[Meeting adjourned at 4:30 p.m.]