FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
73rd Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) Meeting

2-DAY OPEN PUBLIC MEETING

Web-Conference
Silver Spring, Maryland 20993

June 29, 2022

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

ATTENDEES

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Jeannette Yen Lee, Ph.D.	University of Arkansas for Medical Sciences
Sean Morrison, Ph.D.	University of Texas Southwestern Medical Center
Joseph Wu, M.D., Ph.D.	Stanford University
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Paul Conway	Patient Representative
Matthew Cooper, M.D.	Georgetown University School of Medicine
Eric Crombez, M.D.	Ultragenyx Gene Therapy
Jay Fishman, M.D.	Massachusetts General Hospital
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Michael Kawczynski	Food and Drug Administration
PUBLIC COMMENTERS	
Dr. Allan Kirk	American Society of Transplantation
Dr. Jayme Locke	" University of Alabama at Birmingham"

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1 **OPENING REMARKS: CALL TO ORDER AND WELCOME**

2

3 **MR. MICHAEL KAWCZYNSKI:** All right. Good

4 morning. Welcome to the 73rd meeting of the Cellular,

5 Tissue, and Gene Therapies Advisory Committee meeting

6 at FDA. I'm Mike Kawczynski, and I will be helping

7 moderate today's meeting along with the chair, Dr. Lisa

8 Butterfield and our DFO, Christina Vert.

9 Please note, today, this is a live public

10 meeting, so we do have participants, members, and that,

11 from around the world. So, if at any time we make a

12 momentary pause to assist them with any technical

13 issues we will do so, so that you, the consumer, do not

14 miss any of the content.

15 With that being said, I am going to hand it

16 off to our chair, Dr. Lisa Butterfield. Dr.

17 Butterfield, why don't you take it away.

18 **DR. LISA BUTTERFIELD:** Great. Thank you.

19 Good morning, everyone. My name is Lisa Butterfield.

20 And I'd like to welcome all of the members, all of the

21 participants, the temporary members, as well as the

1 public viewing remotely to our meeting today.

2 One bit of housekeeping, please remember to

3 use the raise your hand function. And that's how I see

4 you, and I can call on you to participate in today's

5 important proceedings.

6 So, as we begin, I'd like to introduce

7 Christina Vert, the Designated Federal Officer for

8 today for the administrative announcements. Christina.

9

10 **ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, INTRODUCTION**

11 **OF COMMITTEE, CONFLICT OF INTEREST STATEMENT**

12

13 **MS. CHRISTINA VERT:** Thank you, Dr.

14 Butterfield. Good morning, everyone. This is

15 Christina Vert. And it is my great honor to serve as

16 the designated federal officer, DFO, for today's 73rd

17 Cellular, Tissue, and Gene Therapies Advisory Committee

18 meeting. On behalf of the FDA, the Center for

19 Biologics Evaluation and Research, and the Committee, I

20 am happy to welcome everyone for today's virtual

21 meeting.

1 Today, the Committee will meet in open session
2 to discuss regulatory expectations for
3 xenotransplantation products. The discussion topics
4 include human cells that have had ex vivo contact with
5 animal cells and animal organs and cells for
6 transplantation into human subjects, both of which are
7 xenotransplantation products. Today's meeting and the
8 topic were announced in the Federal Registry notice
9 that was published on May 31st, 2022.
10 I would now like to introduce and acknowledge
11 the excellent contributions of the staff in the
12 Division of Scientific Advisors and Consultants
13 including our director, Dr. Prabha Atreya, who is my
14 backup and co-DFO for this meeting.
15 Other staff are Ms. Joanne Lipkind, Ms. Tonica
16 Burke, and Ms. LaShawn Marks, Dr. Sussan Paydar, and
17 Ms. Karen Thomas, who have provided excellent
18 administrative support in preparing for this meeting.
19 I would also like to thank Mike Kawczynski in
20 facilitating the meeting today. Also, our sincere
21 gratitude goes to many CBER and FDA staff working hard

1 behind the scenes trying to ensure that today's virtual
2 meeting will also be a successful one.
3 Please direct any press and media questions
4 for today's meeting to FDA's Office of the Media
5 Affairs at fdaoma@fda.hhs.gov. The transcriptionist
6 for today's meeting is Ms. Linda Giles.
7 Okay. We will begin today's meeting by taking
8 a formal roll call for the Committee members and
9 temporary voting members. When it is your turn, please
10 make sure your video camera is on and you are unmuted
11 and then state your first and last name, your
12 organization, expertise, or role. And when finished,
13 you can turn your camera off or Mike will turn it off
14 so we can proceed to the next person.
15 Please see the member roster slides in which
16 we will begin with the chair, Dr. Butterfield. Please,
17 go ahead.
18 **DR. LISA BUTTERFIELD:** Thank you. Good
19 morning again, everyone. My name is Lisa Butterfield.
20 I'm the vice president of Research and Development at
21 the Parker Institute for Cancer Immunotherapy. I'm

1 also an adjunct professor of microbiology and
2 immunology at the University of California San
3 Francisco. My expertise is in cancer vaccines, cell
4 therapies, and immune biomarkers.
5 **MS. CHRISTINA VERT:** Thank you. Dr. Ahsan.
6 **DR. TABASSUM AHSAN:** Hi. I'm Taby Ahsan. I'm
7 vice president of cell and gene therapy at City of
8 Hope. My focus is on regenerative medicine
9 applications and immunotherapy.
10 **MS. CHRISTINA VERT:** Thank you. Dr. Bloom.
11 **DR. MARSHALL BLOOM:** My name is Marshall
12 Bloom. I'm the associate director for scientific
13 management at the Rocky Mountain Laboratories of the
14 National Institute of Allergy and Infectious Diseases
15 in Hamilton, Montana. I'm also the chief of the
16 section of the biology of vector-borne viruses. My
17 area of expertise is in virus infections and persistent
18 virus infections.
19 **MS. CHRISTINA VERT:** Thank you. Dr. Fox.
20 **DR. BERNARD FOX:** My name is Bernard Fox, and
21 I'm the Harder Family Chair for Cancer Research at the

1 Early Child's Research Institute at Providence Portland
2 Medical Center in Portland, Oregon. I'm also a member
3 and chief of the institute and head of the Laboratory
4 of Molecular and Tumor Immunology. My focus is on
5 tumor immunology, cancer vaccines, adoptive
6 immunotherapy, and translational cancer immunotherapy.
7 **MS. CHRISTINA VERT:** Thank you. Dr. Lee.
8 **DR. JEANNETTE LEE:** Good morning. My name is
9 Jeannette Lee. I'm a professor of biostatistics and a
10 member of the Winthrop P. Rockefeller Cancer Institute
11 at the University of Arkansas for Medical Sciences.
12 Thank you.
13 **MS. CHRISTINA VERT:** Thank you. Dr. Morrison.
14 **DR. SEAN MORRISON:** Yeah. I'm Sean Morrison.
15 I direct Children's Research Institute at UT
16 Southwestern Medical Center in Dallas. My area of
17 expertise is stem cells in cancer, particularly
18 hematopoietic and mesenchymal stem cells and, of
19 course, transplant in that context.
20 **MS. CHRISTINA VERT:** Thank you. Dr. Wu.
21 **DR. JOSEPH WU:** Yeah. So, I'm Joe Wu. I'm

1 the professor and director at the Stanford
2 Cardiovascular Institute. I'm a cardiologist. My area
3 of expertise is in cardiac stem cells, cardiac gene
4 therapy, and tissue engineering.
5 **MS. CHRISTINA VERT:** Thank you. Now, we will
6 next do roll call of our temporary voting members. And
7 we'll start with Dr. Auchincloss.
8 **DR. HUGH AUCHINCLOSS:** Hi. I'm Hugh
9 Auchincloss. And I'm the deputy director at the
10 National Institute of Allergy and Infectious Diseases.
11 My expertise is in the immune response to
12 xenotransplants.
13 **MS. CHRISTINA VERT:** Thank you. Dr.
14 Basavaraju.
15 **DR. SRIDHAR BASAVARAJU:** Hi. I'm Sridhar
16 Basavaraju. I'm the director of the Office of Blood,
17 Organ, and Other Tissue Safety at the CDC in Atlanta.
18 **MS. CHRISTINA VERT:** Thank you. Mr. Conway.
19 **MR. PAUL CONWAY:** My name's Paul Conway. I
20 serve as the chair of Global and Policy for the
21 American Association of Kidney Patients. I've been a

1 kidney patient for 42 years, waited three years on a
2 transplant list. And I've had a kidney transplant for
3 the past 25 years. Thank you.
4 **MS. CHRISTINA VERT:** Thank you. Dr. Cooper.
5 **DR. MATTHEW COOPER:** Morning everyone. I'm
6 Dr. Matt Cooper. I'm the director of kidney and
7 pancreas transplantation for the Medstar Georgetown
8 Transplant Institute in Washington, D.C. Also,
9 Professor of Surgery at Georgetown University School of
10 Medicine. I also currently serve as the president for
11 the United Network for Organ Sharing.
12 **MS. CHRISTINA VERT:** Thank you. Dr. Crombez.
13 **DR. ERIC CROMBEZ:** Hi. I'm Eric Crombez. I'm
14 chief medical officer for Gene Therapy and Inborn
15 Errors of Metabolism at Ultragenyx. And I'll be
16 serving as the industry representative for today's
17 meeting.
18 **MS. CHRISTINA VERT:** Thank you. Dr. Fishman.
19 **DR. JAY FISHMAN:** Good morning. Jay Fishman.
20 I'm a professor of medicine at Harvard Medical School
21 and associate director of the MGH -- Mass General

1 Hospital -- Transplant Center. My expertise is in
2 transplant infectious disease and particularly in
3 infections associated with xenotransplantation.
4 **MS. CHRISTINA VERT:** Thank you. Dr. Kimmel.
5 **DR. PAUL KIMMEL:** Hi. I'm Paul Kimmel. I'm a
6 nephrologist at NIDDK. Also, clinical professor
7 emeritus at George Washington University. My expertise
8 is in general clinical nephrology.
9 **MS. CHRISTINA VERT:** Thank you. Dr. Maragh.
10 **DR. SAMANTHA MARAGH:** Hi. I am from the U.S.
11 National Institute of Standards and Technology. And
12 there, I lead the Biomarker and Genomic Sciences Group
13 as well as the Genome Editing Program. My expertise is
14 in human genetics and molecular biology, particularly
15 in nucleic acid measurements in genome editing.
16 **MS. CHRISTINA VERT:** Thank you. Ms. Kathleen
17 O'Sullivan-Fortin.
18 **MS. KATHLEEN O'SULLIVAN-FORTIN:** Hi. I'm
19 Kathleen O'Sullivan-Fortin. I'm a co-founder and
20 general counsel of a rare disease nonprofit, ALD
21 CONNECT. And my expertise is in being a rare disease

1 patient and the mother of rare disease patients. Thank
2 you.
3 **MS. CHRISTINA VERT:** Thank you. Dr. Palevsky.
4 **DR. PAUL PALEVSKY:** Hi. My name is Paul
5 Palevsky. I'm a professor of medicine at the
6 University of Pittsburgh School of Medicine, chief of
7 Kidney Medicine at the VA Pittsburgh Healthcare System,
8 deputy national executive director of the VHA National
9 Kidney Medicine Program. I'm a practicing nephrologist
10 dealing with acute kidney injury and general
11 nephrology. And I'm currently president of the
12 National Kidney Foundation.
13 **MS. CHRISTINA VERT:** Thank you. Dr. Zeiss.
14 **DR. CAROLINE ZEISS:** Hi. I'm Caroline Zeiss.
15 I'm a professor of comparative medicine at Yale
16 University. I'm a lab animal vet and motion anatomic
17 pathologist. And my research is predominantly in
18 neuroscientific infectious disease and focused on
19 translation.
20 **MS. CHRISTINA VERT:** Thank you. Thank you for
21 your introductions. I would also like to acknowledge

1 CBER leadership including Dr. Marks and Dr. Bryan who
2 may be present now or joining the meeting at other
3 times.
4 I would now proceed with reading of the
5 conflict of interest statement for the public record.
6 Thank you.
7 The Food and Drug Administration, FDA, is
8 convening virtually June 29th and 30th, 2022, for the
9 73rd meeting of the Cellular, Tissue, and Gene
10 Therapies Advisory Committee under the authority of the
11 Federal Advisory Committee Act, FACA, of 1972. Dr.
12 Lisa Butterfield is serving as the chair for today's
13 meeting.
14 The CTGTAC Committee will meet in open session
15 on both days to discuss the current regulatory
16 expectations for xenotransplantation products. The
17 discussion topics include human cells that have had ex
18 vivo contact with animal cells and animal organs and
19 cells for transplantation into human subjects.
20 On June 29th, 2022, in the morning under
21 Session 1, the CTGTAC Committee will meet to discuss

1 and make recommendations on human cells that have had
2 ex vivo contact with animal cells. In the afternoon
3 under Session 2, the Committee will begin to discuss
4 and make recommendations on animal organs and cells for
5 transplantation into human subjects and their
6 associated risks. The topic is determined to be a
7 particular matter of general applicability, PMGA.
8 With the exception of the industry
9 representative member, all standing and temporary
10 voting and temporary non-voting members of CTGTAC are
11 appointed as special government employees (SGEs), or
12 regular government employees (RGEs), from other
13 agencies and are subject to federal conflict of
14 interest laws and regulations.
15 The following information on the status of
16 this Committee's compliance with federal ethics and
17 conflict of interest laws include, but are not limited
18 to, 18 U.S.C. Section 208 is being provided to
19 participants in today's meeting and the public.
20 Related to the discussions at this meeting,
21 all members, RGE and SGE consultants of this Committee,

1 have been screened for potential financial conflicts of
2 interest of their own as well as those imputed to them,
3 including those of their spouse or minor children and
4 for the purposes of 18 U.S. Code Section 208, their
5 employers.
6 These interests may include investments,
7 consulting, expert witness testimony, contracts and
8 grants, cooperative research and development agreements
9 (CRADAs), teaching, speaking, writing, patents and
10 royalties, and primary employment. These may include
11 interests that are current or under negotiation.
12 FDA has determined that all members of this
13 Advisory Committee, both regular and temporary members,
14 are in compliance with federal ethics and conflict of
15 interest laws.
16 Under 18 U.S. Code Section 208, Congress has
17 authorized FDA to grant waivers to special government
18 employees who have financial conflicts of interest when
19 it is determined that the Agency's need for a special
20 government employee's service outweighs the potential
21 for conflict of interest created by the financial

1 interests involved or when the interest of a regular
2 government employee is not so substantial as to be
3 deemed likely to affect the integrity of the services
4 which the government may expect from the employee.
5 Based on today's agenda and all financial
6 interests reported by Committee members and
7 consultants, no conflict of interest waivers were
8 issued under 18 U.S. Code Section 208 in connection
9 with this meeting.
10 We have the following consultants serving as
11 temporary voting members: Dr. Hugh Auchincloss, Dr.
12 Sridhar Basavaraju, Dr. Matthew Cooper, Dr. Jay
13 Fishman, Dr. Paul Kimmel, Dr. Samantha Maragh, Dr. Paul
14 Palevsky, and Dr. Caroline Zeiss. We have one patient
15 representative, namely Mr. Paul Conway, serving as a
16 temporary voting member.
17 Ms. Kathleen O'Sullivan-Fortin is serving as
18 the temporary consumer representative for this
19 committee meeting. Consumer representatives are
20 appointed special government employees and are screened
21 and cleared prior to their participation in the

1 meeting. They are voting members of the Committee.

2 Dr. Eric Crombez of Ultragenyx Gene Therapy

3 will serve as the alternate temporary industry

4 representative for today's meeting. Industry

5 representatives are not appointed as special government

6 employees and serve as non-voting members of the

7 Committee. Industry representatives act on behalf of

8 all related industry and bring general industry

9 perspective to the Committee. Industry representatives

10 on this Committee are not screened, do not participate

11 in any of the closed sessions, if held, and do not have

12 voting privileges.

13 The guest speaker for today is Dr. Joachim

14 Denner, director of the Institute of Virology at the

15 Free University of Berlin located in Berlin, Germany.

16 Disclosure of conflict of interest for guest speakers

17 follow the applicable federal laws, regulations, and

18 FDA guidance.

19 FDA encourages all meeting participants,

20 including open hearing speakers, to advise the

21 Committee of any financial relationships that they may

1 have with any affected firm, its products, and if
2 known, its direct competitors.
3 We would like to remind members, consultants,
4 and participants that if the discussions involve any
5 other products or firms not already on the agenda for
6 which an FDA participant has a personal or imputed
7 financial interest, the participant needs to inform the
8 DFO and exclude themselves from such involvement and
9 their exclusion will be noted for the record.
10 This concludes my reading of the conflicts of
11 interest statement for the public record. At this
12 time, I would like to hand over the meeting to Dr. Lisa
13 Butterfield. Thank you.
14 **DR. LISA BUTTERFIELD:** All right. Thank you,
15 very much, Christina. So, now -- next, I would like to
16 welcome Dr. Wilson Bryan who's the director of OTAT for
17 the FDA opening remarks. Dr. Bryan, please.
18
19 **FDA OPENING REMARKS**
20
21 **DR. WILSON BRYAN:** Hey. Good morning. And

1 welcome on behalf of the FDA, the Center for Biologics
2 Evaluation and Research, and the Office of Tissues and
3 Advanced Therapies. I want to thank the members of
4 this Advisory Committee for taking the time to consider
5 the topic of xenotransplantation.
6 There are many issues in the field of
7 xenotransplantation that warrant discussion. Over the
8 next two days, we ask this Committee to consider some
9 of the scientific and regulatory issues. For example,
10 we ask this Committee to consider appropriate test
11 methods and control strategies for manufacturing
12 xenotransplantation products, how to control the risk
13 of infectious agent transmission, appropriate
14 monitoring of xenotransplant recipients, and the
15 appropriate range of nonclinical animal studies to
16 support future clinical applications.
17 On the other hand, we are not asking this
18 Committee to discuss other important
19 xenotransplantation issues such as the ethics of
20 xenotransplantation. With that in mind, we recognize
21 that this meeting is part of a continuing public

1 conversation regarding xenotransplantation.

2 We ask this Committee to consider two general

3 categories of xenotransplantation products: products in

4 which human cells have had contact with live animal

5 cells during the manufacture of cellular products and

6 whole organs that are transplanted from animals to

7 humans.

8 The FDA published a guidance on

9 xenotransplantation back in 2003 and updated that

10 guidance in 2016. While the updated guidance addresses

11 many of the issues that will be discussed today, the

12 science is changing rapidly. Particularly, advances in

13 gene editing have given new impetus to the field of

14 xenotransplantation.

15 In addition, recent high-profile cases of

16 transplantation of genetically modified pig kidneys

17 into brain-dead humans and a single case of

18 transplantation of a genetically modified pig heart

19 into a patient with end-stage heart disease and no

20 treatment options have increased public awareness of

21 the field. These specific events are not the subject

1 of this Advisory Committee meeting. However, these
2 events have made this an optimal time for a public
3 discussion that will help to address issues in the
4 field.
5 This meeting will also serve to educate the
6 public and provide transparency regarding the FDA's
7 role in the regulation of xenotransplantation.
8 Considering the limited availability of human
9 organs for transplant, the FDA recognizes the
10 tremendous unmet need for new treatments of patients
11 with end-stage organ failure including, but not limited
12 to, patients with heart failure or kidney failure who
13 have run out of available treatment options.
14 In an editorial last week in the *New England*
15 *Journal of Medicine*, Dr. Elizabeth Phimister discussed
16 the recent pig-to-human heart transplant. Dr.
17 Phimister noted that, "We can be grateful for the
18 patient's willingness to volunteer for this
19 extraordinary test of xenotransplantation and humbly
20 acknowledge the contribution of animal models and
21 animal donors to biomedical research."

1 At the FDA, we want to echo Dr. Phimister's
2 remarks and recognize that as this field advances, we
3 owe so much to the patients and their families, and to
4 the preclinical studies in animal donors.
5 I am very much looking forward to hearing the
6 perspectives and recommendations of this Committee
7 regarding the science and regulation of
8 xenotransplantation. I am also looking forward to the
9 presentations from our guest speakers, to any public
10 comments submitted to the docket and to the statements
11 that we will hear in the Open Public Hearings. All of
12 your deliberations and comments will assist the FDA as
13 we work with the patient and scientific communities to
14 advance the field of xenotransplantation.
15 I will stop there and turn back to Dr.
16 Butterfield to continue with the agenda.
17 **DR. LISA BUTTERFIELD:** Thank you very much for
18 those important comments that set the stage for our
19 important discussion today. So now, we'd like to begin
20 with the FDA presentation of FDA views on
21 xenotransplantation. And I'd like to welcome Judith

1 Arcidiacono for those remarks.

2

3 **FDA PRESENTATION: FDA VIEWS ON XENOTRANSPLANTATION**

4

5 **DR. JUDITH ARCIDIACONO:** Thank you, Dr.

6 Butterfield. My name is Judith Arcidiacono. And I'm

7 the policy expert on xenotransplantation in the Office

8 of Tissues and Advanced Therapies. My presentation

9 will provide introductory information on the topics to

10 be discussed at this Advisory Committee meeting.

11 So, let's begin with the definition of

12 xenotransplantation. Xenotransplantation is any

13 procedure that involves the transplantation,

14 implantation, or infusion into a human recipient of

15 either live cells, tissues, or organs from a non-human

16 animal source or human body fluids, cells, tissues, or

17 organs that have had ex vivo contact with live non-

18 human animal cells, tissues, or organs. This

19 definition can be found in the Public Health Service

20 Guidelines on Infectious Disease Issues in

21 Xenotransplantation as well as the 2016 FDA Guidance on

1 Xenotransplantation.

2 This Advisory Committee meeting is convened to
3 provide the Food and Drug Administration,
4 xenotransplantation product developers, and
5 stakeholders with insights and perspectives regarding
6 requirements to ensure the efficacy and safety of
7 xenotransplantation products.

8 Topics for discussion include infectious
9 disease risks associated with xenotransplantation
10 products and porcine donor animals and how to assess
11 these risks; infectious disease testing for
12 xenotransplantation products that have had ex vivo
13 contact with animal cells; strategies for meeting
14 regulatory requirements for identity, purity, and
15 potency of xenotransplantation products; current
16 strategies to control xenotransplant rejection by gene
17 modification of donor animals and by systemic immune
18 suppression of human recipients; characterization
19 studies to ensure the function of the pig organs before
20 and after transplantation.

21 There are two FDA centers responsible for

1 regulatory oversight of xenotransplantation. The
2 Center for Veterinary Medicine, or CVM, is responsible
3 for oversight of intentional genetic alterations in
4 animals. The Center for Biologics Evaluation and
5 Research, or CBER, is responsible for oversight of non-
6 human organs, cells, and tissues transplanted into
7 human recipients.
8 Due to the complexity of xenotransplantation
9 products, the review team is comprised of experts from
10 multiple FDA centers and offices. The basic review
11 team consists of members of the Office of Tissues and
12 Advanced Therapies which is enhanced with members of
13 the CBER's Offices of Compliance, Veterinary Science,
14 Statistics and Epidemiology, and current good
15 manufacturing practice experts.
16 Depending on the nature of the product, other
17 FDA centers may be involved in reviewing
18 xenotransplantation clinical trial documents. If
19 intentionally genetically altered animals are used,
20 then experts from CVM are consulted. If a device is
21 part of the product, then the Center for Devices and

1 Radiological Health is consulted.

2 If the investigation of a new drug is involved
3 in the xenotransplantation clinical trial, then the
4 Center for Drugs Evaluation and Research may be
5 consulted. And from time to time, an expert on a
6 scientific policy issue such as a clinical trial for a
7 specific patient population may be included in the
8 review too.

9 Outside consultants such as those who are
10 serving on this panel of experts for this meeting may
11 be involved in evaluating proposed clinical trials.
12 These experts may include scientific experts, medical
13 experts, patient advocates, and ethicists.

14 There are many risks associated with the use
15 of xenotransplantation products. From the public
16 health perspective, the primary concerns are the
17 transmission of known and unknown pathogens and the
18 risk of zoonotic infections to patients, their personal
19 contacts, health care professionals, and the public.
20 Keeping in mind that we can only test for pathogens
21 that we know of at the time of testing, selecting and

1 archiving of animal and patient samples is important.
2 And I will discuss this later in more detail.
3 The recipient may have adverse inflammatory
4 and immunological responses to donor cells or molecules
5 secreted by donor cells. In addition, there may be
6 adverse effects associated with the recipient's
7 rejection of donor animal cells, tissues, or organs.
8 Other risks include physiologic and metabolic
9 incompatibilities between donor organs and the
10 recipient's organs and adverse effects of
11 immunosuppressive agents.
12 Humans and pigs are not closely related
13 biogenetically. Therefore, a rigorous rejection
14 response is expected. And therefore, an intense
15 immunosuppression regimen may be required.
16 The 2016 CBER Xenotransplantation Guidance
17 states that human cells that have had ex vivo contact
18 with non-human cells, tissues, or organs are
19 xenotransplantation products. Examples of such
20 products are human cells co-cultured with irradiated
21 and inactivated, well-characterized animal cell lines;

1 human cells co-cultured with irradiated or inactivated
2 primary or freshly isolated animal cells; and human
3 cells that are perfused through a device containing
4 live animal cells. These different types of products
5 present different levels of perceived risk to the
6 recipient.
7 Co-culturing human cells with well-
8 characterized animal cell lines present the lowest risk
9 of infectious disease transmission to the recipient
10 mostly because cell banks can be readily tested, and
11 requirements for cell lines have been worked out over
12 time.
13 Co-culture with primary animal cells is of
14 higher risk as the derivation of these cells rely on
15 appropriate human husbandry and other safety measures
16 that I will discuss later in this presentation.
17 Perfusion with animal cells is of the greatest
18 risk because of the amount of time that the patient
19 cells are exposed to animal cells. Co-culture with
20 animal cells and perfusion both rely on the health and
21 suitability of donor animals, specifically the absence

1 of potentially infectious diseases.

2 FDA would like the Committee to consider the

3 use of well-characterized mouse cell lines as feeder

4 cells where the history of derivation is well known.

5 Examples of such products include two FDA-approved

6 products, Epicel and Stratagraft.

7 We also ask the Committee to consider whether

8 current analytical technologies are sufficiently

9 sensitive to allow for flexibility and less stringent

10 archival requirements and recipient deferrals from

11 donating cells, tissues, or organs.

12 In addition, we ask the Committee to discuss

13 factors that may permit the application of regulatory

14 flexibility for other products that have had ex vivo

15 contact with animal cells like co-culture or perfusion.

16 To reduce the risk of transmission of

17 infectious disease from source animals to patients, FDA

18 has built in multi-layers of safety into the

19 expectations for sourced animals. These expectations

20 include the following. Animal cells should be bred

21 from closed herds of known origin, preferably in the

1 United States. Animal health should be maintained by
2 regular health assessments, vaccination programs, et
3 cetera.
4 Procedures should be in place to minimize
5 infectious disease risk. Such procedures include
6 conducting organ harvest in appropriate environments;
7 screening for infectious agents prior to
8 transplantation; quarantine of donor animals prior to
9 harvesting; documenting the harvesting and handling of
10 pig cells, organs, and tissues; and collecting and
11 archiving of samples pre-harvest and post-harvest.
12 The PHS Guidelines and the FDA Guidance on
13 Xenotransplantation provide recommendations on the
14 collecting, harvesting, and storage of animal and human
15 samples.
16 Samples from donor animals should include
17 portions of the harvested cell, tissue, or organ;
18 samples from major organ systems at necropsy;
19 collection of plasma and leukocytes. And these samples
20 should be collected at pre-determined intervals prior
21 to harvest, at the time of harvest, and post-mortem.

1 For the recipients, blood, plasma, saliva, and
2 leukocytes should be collected pre-transplant, post-
3 transplant, at pre-determined intervals, and post-
4 mortem.
5 The samples collected are for use by the
6 Public Health Service for recipient diagnosis and care
7 and for the FDA. Herd records and samples should be
8 stored for 50 years. A backup plan for storing records
9 and samples should be in place in case the sponsor goes
10 out of business.
11 Storage conditions of samples is important to
12 be sure that there is a linkage between patient samples
13 and donor animal samples. Samples should be stored in
14 media appropriate for RNA, DNA, cell viability, and
15 antibody preservation. Pigs are the preferred source
16 for xenotransplantation. This is because their organs
17 are similar in size to humans.
18 So now, I will focus on porcine viruses of
19 concern in xenotransplantation. And I just want to
20 note, this is a short list: porcine endogenous
21 retrovirus or PERV, porcine circovirus or PCV, PHLV

1 [sic] porcine lymphotropic herpes virus, and porcine
2 herpes virus. I have to apologize; I'm having problems
3 with the slides.
4 Porcine endogenous retrovirus or PERV is --
5 they are type C gamma retroviruses, and there are four
6 subtypes. PERV A infects human and pig cells, PERV B
7 also infects human and pig cells, PERV A/C recombinants
8 infect human cells and have been reported to be 500-
9 fold more effective than PERV A alone.
10 Porcine circovirus or PCV -- there are three
11 species. PCV 1 does not cause disease in pigs. PCV 2
12 causes post-weaning multi-systemic weaning syndrome.
13 PCV 3 causes porcine dermatitis and nephropathy
14 syndrome, reproductive failure, as well as cardiac and
15 multisystemic inflammation. PCV 3 transmission has
16 been observed in some pig-to-baboon orthotopic heart
17 transplants.
18 Porcine cytomegalovirus, PCMV, and porcine
19 roseolovirus are also of concern. PCMV is closely
20 related to human herpesvirus 6 and 7. Human HCMV
21 causes fatal infections in human organ transplant

1 recipients. PCMV transmission has been observed in pig
2 orthotopic heart transplants in baboons and is
3 associated with reduced survival time of recipient
4 baboons.
5 Porcine lymphotropic herpes virus or PLHV is a
6 gamma herpes virus that is widespread in pigs and
7 closely related to the Epstein-Barr virus and Kaposi
8 Syndrome virus, which cause serious disease in humans.
9 PHLV 1 is associated with post-transplant
10 lymphoproliferative disease or PTLD in experimental
11 transplants in minipigs. PTLD is also a complication
12 of human allotransplant and is linked to EBV.
13 Examples of methods to detect infectious
14 disease vary and here is a short list of those methods:
15 non-specific in vitro adventitious virus tests with
16 indicator cell lines, polymerase chain reaction, next-
17 generation sequencing, infectivity assays, Western
18 blot, and ELISA. As with any biologics,
19 xenotransplantation products should be characterized
20 with regards to identity, purity, potency, and
21 sterility.

1 CMC, or chemistry manufacturing control,
2 include process controls or current GMPs. And that
3 would be procedures put in place, reagents, and test
4 methods for controlling infectious disease
5 transmission; controls for tracking, labeling, and
6 cross-contamination; conditions for processing, storage
7 and shipping.
8 Product characterization would include
9 identity, purity, and potency, and I'll talk a little
10 bit more about that in the next slide. Safety testing,
11 that would include infectious disease testing and
12 sterility testing. And, if possible, virus
13 inactivation or removal is recommended. The testing of
14 cells and tissues and organs depends on the product
15 type. And so, in the next few slides, I will discuss
16 the different testing strategies.
17 Characterization for cells that have been
18 cultured, harvested, processed, and stored --
19 characterization would include identity of desired
20 stored cell type; purity, which would be the presence
21 of desired cell types and contaminating cell types.

1 The potency assays used should measure and reflect the
2 intended activity of the cell or tissue type. Of
3 course, testing for infectious disease is required.
4 All of the cell culture procedures and
5 reagents used for culturing, harvesting, and storing
6 the cells or tissues should be qualified, and they
7 should be tested and maintained for sterility. A plan
8 should be in place for in-process testing as well as
9 final product testing.
10 Whole organ testing is a little bit more
11 challenging and requires a little bit of creativity.
12 Examples of identity testing could be scans of the
13 organ to be transplanted. Purity or testing for
14 adventitious agents can be done via biopsy to determine
15 the cell and tissue types as well as the presence of
16 infectious agents. Potency testing could be a measure
17 of physiological function tests and laboratory
18 measurements of organ function.
19 Sterility and viral testing sampling is
20 important due to the trophism of certain viruses. So,
21 you want to make sure that you are testing the organ

1 that may harbor the virus. Testing of donor animal
2 prior to organ harvest is recommended, and we recommend
3 you consult FDA on your testing strategy.
4 Strategies to control rejection can be at the
5 animal level or the patient and recipient level.
6 Animals with intentional genomic alteration would
7 include knocking out of pig antigens that induce the
8 production of human antibodies or knocking in or
9 expression of human genes that prevent vascular injury
10 and cell-mediated rejection.
11 From the patient side, administration of
12 targeted immunomodulatory drugs in combination with
13 genetic alterations are improved strategies to control
14 rejection. Examples of that would be blocking co-
15 stimulatory pathways with monoclonal antibodies such as
16 CTLA4, the use of calcineurin-inhibiting drugs such as
17 tacrolimus, and T and B cell inhibitors such as anti-
18 thymocyte globulin (ATG), and rituximab.
19 However, there is a lot of information that is
20 still needed. What are the numbers and types of
21 genetic alterations needed, and are these organ-

1 specific requirements? We also don't know what the
2 correct balance between intentional genetic alterations
3 and systemic immunosuppression of the recipient. In
4 addition, we are unclear of the effects of human
5 immunosuppressive drugs on the animal organ.
6 I'd like to conclude by stating that advances
7 in understanding xenotransplant rejection and
8 technologies enabling genetic modification of pigs for
9 xenotransplantation have moved the field closer towards
10 initiating clinical trials.
11 As I pointed out, many questions remain with
12 respect to infectious disease transmission; the effect
13 of intentional genetic alterations on the donor cells,
14 tissues, and organs of the pig; and the use of systemic
15 immunosuppression of the patient/recipient of the
16 xenotransplant product.
17 And I would like to thank you for your
18 attention.
19
20 **Q&A SESSION**
21

1 **DR. LISA BUTTERFIELD:** Terrific. Thank you,
2 very much. So, we now have some time for some
3 questions. And I'd like to remind our Committee
4 members and temporary members and everyone to raise
5 that hand. And that's what I'll be looking for. But
6 we have an important opportunity here to have questions
7 from the FDA presentation. Okay. Thank you, very
8 much. The first question is from our guest, Dr.
9 Fishman.
10 **DR. JAY FISHMAN:** Thanks. That was a
11 tremendous summary of a huge amount of material, so job
12 well done. I think it's important to emphasize in
13 thinking about this the fact that although we've -- and
14 I -- have detected many of these viruses in pigs that
15 most, if not all of them, have not been shown to infect
16 normal human cells. And I wonder how you build that
17 into the equation. In other words, in vitro or in vivo
18 studies with human cells that are not transformed or
19 not indicator cell lines, is that important or is just
20 the presence of the virus enough to raise our anxiety?
21 **DR. JUDITH ARCIDIACONO:** So, I think it's

1 important to remember that a patient receiving
2 xenotransplant is highly immunocompromised, probably
3 not just from the disease, but the immunosuppressants
4 and other drugs that they may be given.
5 **DR. JAY FISHMAN:** Yeah. And the fact is, of
6 course, they're going to have a graft for a prolonged
7 period of time, hopefully, to replace organ function.
8 But I think it would be nice to think about the
9 biologics, the mechanistic questions as to whether or
10 not all pathogens are created equal or whether or not
11 some pathogens are more or less likely to be
12 significant in that setting as we've found in
13 allotransplantation.
14 **DR. JUDITH ARCIDIACONO:** Yeah. And so, I'd
15 just like to note that PERV detection has only happened
16 in vitro. And there have been no evidence of PERV
17 transmission in pre-clinical studies, or there have
18 been some studies with encapsulated outlets done years
19 ago. So, you know, I think we would like for the
20 Committee to talk about, what are the real and
21 perceived risks to infectious disease? And there are

1 also some new emerging diseases that have recently
2 shown up in the literature without a lot of
3 information.
4 And also, the testing strategies used -- so,
5 you have to make sure you're testing the risk organs or
6 tissues. And you also have to have some understanding
7 of the trophism with respect to the body, you know,
8 where it's going to land. And so, some of these
9 viruses that are emerging, we may not have enough
10 information yet. So, the archiving and storing of
11 samples is really going to be important.
12 **DR. LISA BUTTERFIELD:** Great. Thank you very
13 much, for that. And next, I'd like to call on our
14 patient representative, Paul Conway, please.
15 **MR. PAUL CONWAY:** Great. Thank you, very
16 much. Quick question for you. First, a compliment.
17 Very thorough presentation. There was one thing that
18 caught my ear as you were speaking that was not in the
19 notes. And that was in terms of herds of known origin.
20 And I believe that you said preferably U.S., and I was
21 wondering if you could elaborate on that.

1 Because I think one of the questions that's
2 out there with the patient community is as you take it
3 to look at this, what are some of the risks, especially
4 supply chain and that type of thing? But I was
5 particularly interested in the preference that you may
6 have noted in your comments. Thank you.
7 **DR. JUDITH ARCIDIACONO:** So, it's really good
8 for us that we can derive pigs through c-section and
9 then carry them through generations in a very clean
10 environment. And we explain this in detail in the 2016
11 FDA Guidance on Xenotransplantation. And in the
12 beginning -- and there are still groups out there
13 thinking that they may use other animals. So, if
14 you're going to use non-human primates or bovine as
15 source animals, you would want those to come from the
16 U.S. where we have some assurance that the animals do
17 not harbor viruses.
18 Because, you know, the viruses could depend on
19 geographical location. So, if you were to go back to
20 when we were all worried about the bovine brain and the
21 issues with viruses that could be transmitted through

1 eating beef, the ideas about having the animals bred in
2 the U.S. is where that comes from.
3 **MR. PAUL CONWAY:** Thank you.
4 **DR. LISA BUTTERFIELD:** All right. Thank you
5 as well for that exchange. So, I'm looking for -- we
6 have a little bit more time. So, are there other
7 questions based on these comments? Great. I'm going
8 to call on Marshall -- Dr. Bloom, please.
9 **DR. MARSHALL BLOOM:** Judy, thank you for that
10 very, very comprehensive and thorough presentation.
11 It's an excellent summary of a voluminous amount of
12 information. The one thing that I would like to note
13 is that you talk about increasing risk based on cells
14 of known origin, primary cells, perfusion, and then the
15 whole organ transplantation.
16 And it seems to me that a lot of the issues
17 that you're asking the Committee to talk about, the
18 answers to those questions are very, very different for
19 each of those different layers of risk, going from
20 well-characterized cells lines to xenotransplantation
21 of say a kidney or a heart.

1 So, in some ways, that sort of -- the amount
2 of information is so great and the considerations for
3 each of those different levels are really, really
4 significant. So, I'm hopeful that we'll be able to
5 give you all some useful information because it's very,
6 very different. Thanks.
7 **DR. JUDITH ARCIDIACONO:** Yeah. And so, we
8 recognize that the risks are different. And there are
9 two products that I mentioned, Epicel and Stratagraft,
10 that have been FDA approved. And those were well-
11 characterized cell lines. And so, the requirements for
12 archiving and storage, that could be really burdensome.
13 So, we really want to know, what is a reasonable amount
14 of burden to put on the sponsors who produce these
15 different products?
16 **DR. MARSHALL BLOOM:** Yeah. Thank you.
17 **DR. LISA BUTTERFIELD:** All right. Let's next
18 go back to Dr. Fishman.
19 **DR. JAY FISHMAN:** Yeah. A question that
20 follows up on Dr. Bloom's and relates to archiving,
21 which is obviously, as you just said, a burden on

1 whoever's performing clinical trials of various types.
2 I wonder about the value of 50 years or such prolonged
3 periods of archiving. And the reason is the following,
4 in allotransplantation, we don't see infections related
5 to the donor emerging that late. There is always a
6 possibility, of course, but it seems like in the
7 longest possible time.

8 And I'm wondering where the 50-year mark came
9 from and whether that might something where we could
10 think a little bit about together, about how to make
11 that more manageable for sponsors of clinical trials,
12 for example.

13 **DR. JUDITH ARCIDIACONO:** Yeah. So, Dr.
14 Fishman, you may remember back when we were developing
15 our policy on xenotransplantation some time ago, we
16 were in the era of the AIDS epidemic. And so, we were
17 maybe really cautious at that time. And so, we've had
18 others talk to us about, is 50 years really sufficient?
19 And so, when a sponsor comes to the Agency, we'll have
20 a discussion about long-term follow-up and what we feel
21 is reasonable to protect the public health.

1 And as you know, we may be collecting samples
2 from our patient today, and ten years from now we
3 identify an infectious disease risk this patient may
4 have passed. But we might want to have to look back
5 and see, well, how long has this virus existed? And
6 technology improves over time and things like that.
7 So, that's where we were coming from with the 50 years.
8 But again, it's another issue that we would like the
9 Committee to give us some advice on what they think is
10 reasonable.
11 **DR. JAY FISHMAN:** Thank you.
12 **DR. LISA BUTTERFIELD:** All right. Well, thank
13 you, very much. Some good beginnings to our
14 discussions today. Do we have -- I think we have one
15 more question from Taby Ahsan. Dr. Ahsan, please.
16 **DR. TABASSUM AHSAN:** Thanks. Just a quick
17 question to follow up on the archiving. So, what's our
18 history on that? What's the longest sample that we've
19 stored? And has there been value from the data from
20 testing that sample?
21 **DR. JUDITH ARCIDIACONO:** So, once FDA --

1 there's kind of a story here. Once FDA put out the
2 2003 originally, revised in 2016, guidance, we saw a
3 huge decline in xenotransplantation activity. So, all
4 we really had were products that met the definition of
5 xenotransplantation through co-culturing. We don't
6 have real data with viable cells. They were mostly
7 cells that have been exposed. And many of those trials
8 went away over 20 years ago, and the samples were lost
9 because something happened. So, that's what happened.
10 But I think it will -- some of the companies
11 of the approved products, they have submitted data to
12 use that made us confident that we could adjust the
13 expectations. I don't see that happening with viable
14 cells, tissues, and organs being transplanted because
15 we don't have data to say that our expectations should
16 be relaxed.
17 **DR. TABASSUM AHSAN:** Yeah. No, thank you.
18 Because, I mean, I do think it's important to think
19 about not only what we would want but what is realistic
20 and what actually has utility as we make this
21 expectation of this request to think about storing

1 samples for half a century where it needs to be tracked
2 and the sponsor may come and go. I know there was some
3 reference that sponsors must make a plan for what they
4 would do for the archiving of samples if they were to
5 go out of business. But we have to think a little bit
6 realistically as well just because the burden may very
7 much outweigh the utility. Thank you for setting it
8 straight.

9 **DR. JUDITH ARCIDIACONO:** Of course.

10 **DR. LISA BUTTERFIELD:** All right. I'd like to
11 thank everyone for that initial back and forth. And
12 now, I'd like to welcome our next speaker. An invited
13 presentation on Emerging Zoonotic Diseases. Dr.
14 Denner.
15

16 **INVITED SPEAKER PRESENTATION: EMERGING ZOONOTIC**
17 **DISEASES**
18

19 **DR. JOACHIM DENNER:** Hello. Good afternoon
20 from Berlin in Germany. I would like to thank you that
21 you give me the opportunity to share our experience

1 concerning the biosafety of xenotransplantation. My
2 first talk today will be concerning emerging zoonotic
3 diseases. Can I move my slide, please?
4 **MR. MICHAEL KAWCZYNSKI:** You can move your --
5 hold on one second, sir. I'll make sure you can get
6 your slides there. Hold on, one second. My apologies.
7 There you go, sir. You should have the arrows right
8 now. Take it away. Do you see it?
9 **DR. JOACHIM DENNER:** We have, in the past, a
10 lot of emerged diseases. I remind you, AIDS, MERS,
11 Ebola, COVID-19, and now Monkeypox virus infection.
12 And concerning xenotransplantation, we, unfortunately,
13 have a disease, the transmission of the porcine
14 cytomegalovirus or the porcine roseolovirus through the
15 first patient receiving a pig heart. But I hope that
16 this is the first case and will never be repeated.
17 And therefore, I would like to change the
18 topic of my talk a little bit and will speak about pig
19 viruses posing a risk to xenotransplantation and how to
20 eliminate them. I still can't -- oh, I'm sorry.
21 The pig virome is a whole number of viruses in

1 the pig is badly analyzed. Here are two examples from
2 a recent review of mine. And you see that there are a
3 lot of viruses in healthy pigs, in diseased pigs, in
4 Swedish pigs, in Chinese pigs. And it’s mainly
5 picornaviruses and circoviruses.
6 But you see immediately that next-generation
7 sequencing doesn’t show us, for example, the porcine
8 cytomegalovirus which is indeed a risk for
9 xenotransplantation because this network only allows to
10 screen viruses which are in high concentrations and not
11 the actually relevant viruses.
12 There are two known zoonotic -- and zoonotic
13 means known inducing disease viruses. The first is the
14 hepatitis E virus which can be transmitted from pig to
15 humans by eating undercooked pork, by contact, and even
16 by organ from human to human by blood transfusion.
17 The virus induces a chronic infection in
18 immunocompromised humans and disease in individuals
19 with preexisting liver diseases. There is a treatment
20 with Ribavirin, and there is no vaccine, at least in
21 western countries; there is one in China.

1 The second is the porcine cytomegalovirus, or
2 better the porcine roseolovirus because it is closely
3 related to the human herpes viruses 6A, B, and 7 and is
4 only distantly related to the human namesake which
5 represents indeed a great risk in allotransplantation.
6 And I'm sure that this virus contributed to
7 the death of the Baltimore patient. And we should --
8 in fact, will go into detail a little bit later. A
9 significant reduction of transplant survival in non-
10 human primate transplantation. There is no treatment.
11 The drugs against the human cytomegalovirus do not work
12 with the porcine cytomegalovirus. And there is no
13 vaccine.
14 Now, in review. In 2015, I summarized the, at
15 that time, known results concerning transplantation of
16 pig kidneys into baboons and cynomolgus monkeys
17 published by these groups. And you'll see on the first
18 graph, without PCMV, there was a survival time around
19 50 -- 40, 50, and, with PCMV, only 12 days. So it is a
20 significant reduction of the survival time.
21 And we have studied this effect in orthoptic

1 heart transplantation surgery performed with our
2 colleagues in Munich -- a genetically modified pig's
3 heart transplanted to baboon orthotopically. And we
4 immediately saw that the survival time of organs with
5 the virus was significantly lower compared with the
6 survival time of the virus-free animals. And we
7 achieved record times -- 185 days of survival in
8 baboons.
9 And we found that in the animals, the IL-6 and
10 the TNF alpha were up regulated. And the tissue-type
11 plasminogen activator and plasminogen activator
12 inhibitor 1, these complexes were up regulated. So,
13 there was a complete loss of the pro-fibrinolytic
14 properties. The coagulation was disturbed. And we had
15 the opinion that there was a general organ failure
16 after this virus transmission.
17 At the moment, it is still unclear whether
18 PCMV/PRV infects the cells of the baboon or infects the
19 cells of the humans. We have a high virus load in
20 different organs of the baboon with the transmitted
21 virus. We have a very high virus load in the pig heart

1 after explanation, and this clearly indicates that the
2 main replication of the virus took place in the pig
3 heart. The virus load is higher compared to the organ
4 of the donor pig, and this suggests that outside the
5 immune system of the pig now replicates the virus in
6 the pig heart.
7 We investigated the presence of virus-
8 producing cells in the pig heart. You see there are
9 enormous production in different organs of the baboon.
10 You see positive cells in all organs, but we have no
11 evidence that it infects these cells, which suggests
12 that the virus protein may interact with the immune
13 cells and with the endothelial cells and use these
14 changes.
15 Let's come to the porcine endogenous
16 retroviruses because these viruses are integrated in
17 the genome and, as already was stated, we have PERV-A
18 and B which is present in all pigs. PERV-C is present
19 in most but not all pigs. We have recombinants between
20 A and C, and these have very increased titer. They can
21 infect human cells, and they can also replicate immune

1 cells. During this adaptation on human cells, there
2 are changes in the long terminal repeat of the virus
3 which are regulatory sequences. And they were
4 additional binding factor sites for transcription
5 factors.
6 So, retroviruses in general are well known to
7 induce tumors, leukemia. For example, the closest
8 relative to the porcine endogenous retrovirus is feline
9 leukemia virus, murine, and the koala retrovirus. And
10 they are able to induce immunodeficiency not only HIV
11 and SIV but all those gamma retroviruses related to the
12 porcine endogenous retrovirus.
13 And the transspecies transmission of
14 retrovirus is very common. HIV-1 and HIV-2 are the
15 result of the transmission of the human
16 immunodeficiency virus two times. The koala retrovirus
17 is a result of the transmission from bats or rodents.
18 So, this is very common.
19 And we then started to investigate whether
20 pigs are able to release viruses able to infect humans
21 -- human-tropic viruses. And we studied different

1 minipigs -- Göttingen minipigs, Black Forest minipigs,
2 Aachen minipigs, and we also studied German Landrace
3 pigs. And we found only in one case the virus able to
4 infect human 293 cells.
5 But I have to underline that human 293 cells
6 are very susceptible to the porcine endogenous
7 retrovirus because they lost all the intracytoplasmic
8 regulator proteins which can prevent virus infection.
9 And if I detected all at PERV-C, we saw only a
10 very few numbers of recombinant in the genome of some
11 cells, but no release of virus. And this was the only
12 case we could see.
13 In the past, there were many attempts to find
14 an animal model for PERV infection to study it. For
15 example, in small animal transplantation infection
16 experiments, with either with and without
17 immunosuppression, they were all negative. But we have
18 to add that some of these animals lack the PERV
19 receptor.
20 In pig-to-non-human primate transplantation
21 and other infection experiments in my laboratory, all

1 were no transmission. But we have to confess that the
2 receptor in non-human primates does not fit well.
3 Most important are the first clinical trials
4 with islet cells in New Zealand and Argentina. They
5 were all negative. But, of course, over the years,
6 this is not in vascularized organ, and there was less
7 immunosuppression because they were encapsulated, these
8 islet cells.
9 In the past, numerous laboratories started to
10 analyze and characterize pigs which were developed for
11 xenotransplantation. And the first were the Auckland
12 Island Pigs which were used in New Zealand and
13 Argentina for the islet cell transplantation. These
14 are the microorganisms screened for. No transmission
15 in all patients. We checked all the patients. No
16 transmission even not PERV. But PERV, of course, was
17 present in all ten pigs.
18 Then in another laboratory, there were
19 numerous other viruses detected in the pigs, but they
20 were not transmitted. And similar results here and
21 here.

1 We tested the Göttingen minipigs because it is
2 planned to use them in Germany as the source for islet
3 cell transplantation for diabetic patients. And we
4 tested 88 microorganisms. We found that some animals
5 were positive for PCMV, hepatitis E, PLHV-1, and PCV2.
6 And of course, all were positive for PERV-C with the
7 risk for A/C recombination.
8 And when we now look at the results of the
9 first clinical and pre-clinical trial, the Auckland
10 Island pigs, there were pre-clinical trials. In
11 cynomolgus monkeys, no transmission of PERV and other
12 porcine virus. The same in the clinical trials, no
13 transmission. When encapsulated cells from diseased
14 animals, they transmitted the homologous viruses. We
15 had no transmission of virus despite the fact that
16 these viruses were present in the donor pigs.
17 In another case, no transmission despite the
18 fact that PCMV was in the donor pig, indicating that
19 the immune system is excellent to prevent such virus
20 infection.
21 Another example, islet cells microencapsulated

1 into cynomolgus monkeys, no transmission of pig
2 viruses. The only transmission was the transmission of
3 PCMV I already reported.
4 And we had a case of PCV3 transmission during
5 orthotopic heart transplantation into baboon. And you
6 see that this transmission was observed in the animal
7 with the longest survival time. And due to the long
8 survival time, there was replication of the virus
9 either in the baboon or in the transplant, we don’t
10 know. This is the virus load in the pig before
11 transplantation. This is in the explanted pig heart.
12 This is in different organs of the baboon. Maybe
13 without the virus, they would have lived much longer.
14 In order to eliminate porcine viruses which
15 represent a risk for xenotransplantation, we developed
16 a so-called elimination program. So, if the pig is
17 negative, it can be used immediately for
18 xenotransplantation. If you have a high virus load,
19 you should eliminate this virus. But in the case you
20 have a low virus load and no negative animal, you
21 should try either by vaccination, by treatment with

1 antivirals, or by cesarean delivery, early weaning, and
2 embryo transfer to obtain virus-free animals.
3 You have to keep them isolated in order to
4 prevent re-entry of the virus. And then you have
5 virus-free breeding and xenotransplantation. And of
6 course, there should be screening using sensitive
7 detection methods in order to make clear that the
8 animals are clean.
9 And we performed such an experiment together
10 with our colleagues in Munich. We had ten sows, seven
11 of them were PCMV positive from a facility in Germany.
12 We brought them to a new facility in Munich. And using
13 early weaning, they were allowed to suckle colostrum,
14 but then their mothers were removed. They received
15 milk replacement feeding. And we tested over two years
16 all the piglets with a high number of tests to make
17 sure the virus was gone. And those were at a facility
18 with virus-free animals concerning PCMV/PRV. This is
19 easy to do.
20 And it is not so easy in the case of the
21 porcine endogenous retroviruses because these viruses

1 are in the genome. You cannot eliminate them easily.
2 We had a different strategy. For example, we developed
3 a vaccine based on neutralizing antibodies against the
4 transmembrane and surface envelope protein.
5 Unfortunately, as I already said, there is no animal
6 model. But we showed that a similar vaccine against
7 the feline leukemia virus protected cats for leukemia.
8 There are antiviral drugs can be used. siRNA
9 can be used to reduce the expression of the virus. We
10 showed this in transgenic pigs. And the next step is
11 genome editing and grouping. The right pig was very
12 successful to produce in pigs with inactivated PERV.
13 And simply a short slide showing that we have
14 inhibitor of the reverse transcription. We have
15 inhibitor of the integrase which can prevent the
16 replication side of PERV. We still do not have entry
17 inhibitors or inhibitors of protease but that can be
18 developed so that antiviral drugs can be used in the
19 case of the porcine endogenous retrovirus.
20 And this shows us the treatment of embryonic
21 fibroblast with CRISPR/Cas. The virus is inactivated

1 in highly conserved regions, the polymerase regions.
2 It proves it really cuts all different viruses which
3 are between 26 and 60 in the genome of the pig. And
4 then you can introduce this in all slides a little bit
5 later, and they obtained newborn pigs with inactivated
6 PERV. However, in these cells, they still produced the
7 virus. This virus, it can infect human cells. But if
8 we cannot integrate, then this stops the replication
9 cycle.
10 But the question is, do we need such a
11 CRISPR/Cas treatment? As I already said in the
12 beginning, until now, we have no transmission of PERV
13 observed in animals and in humans treated with pig
14 material. We are not sure if it's off-target effects
15 of CRISPR/Cas. And there is often risk of in-breeding
16 if you want to have a lot of animals with inactivated
17 PERV. But this was (inaudible) in several of our
18 contributions.
19 Last but least, I would like to thank my co-
20 workers at the Free University and at the Robert Koch
21 Institute where I worked before and all our national

1 and international cooperation partners. And I would
2 like to thank you for your attention.
3
4 **Q&A SESSION**
5
6 **DR. LISA BUTTERFIELD:** Terrific. Thank you,
7 very much, Professor Denner, for all the very important
8 data for us to consider. So, we now have about ten
9 minutes or so for questions for clarification and
10 additional information from Professor Denner from our
11 committee members. So, I'm watching for those raised
12 hands. And let's start with Dr. Zeiss, please.
13 **DR. CAROLINE ZEISS:** Hi. Dr. Denner, thank
14 you very much for that. I have a question about
15 porcine cytomegalovirus testing. In the pig-to-human
16 transplant that was reported this year, CMV was tested
17 for in the donor heart by PCR and found to be negative.
18 It was then identified in the patient using microbial
19 cell-free DNA sequencing and appeared to elevate over
20 time once the patient was deceased. It was not
21 identified in the heart afterwards. Although it was

1 not reported, it was tested with PCR.

2 I wonder if you could comment on the

3 respective sensitivity of these methods and possible

4 cross-reactivity with human herpes virus 6?

5 **DR. JOACHIM DENNER:** When you really come to

6 my second talk, I will discuss it in detail and show

7 how our strategies -- but in brief, it is a latent

8 virus. And at a certain time point, you are unable to

9 detect the virus using PCR. So, you have to use

10 immunological methods which were developed and

11 published in 2016. And using these methods, you can

12 easily detect if the animal is infected.

13 **DR. CAROLINE ZEISS:** Great. Thank you.

14 **DR. LISA BUTTERFIELD:** Thank you very much.

15 Next, we have a question from Dr. Fishman.

16 **DR. JAY FISHMAN:** Very nice summary of a lot

17 of work, Joachim. So, thank you. Just for clarity,

18 you made the point that none of the viruses that you

19 described other than hepatitis E and probably swine

20 influenza are known to infect human cells -- normal

21 human cells. So, all of the other viruses are thought

1 to infect the pig xenograft alone to the best of our
2 knowledge. Is that right?
3 **DR. JOACHIM DENNER:** I would say so. In the
4 case of the hepatitis E virus, we know that it can
5 infect human cells. And this is a well-known zoonotic
6 virus. In the case of the porcine
7 cytomegalovirus/porcine roseolovirus, which I call it
8 now to make the difference, we do not know whether it
9 can infect human cells.
10 But we know that it is zoonotic. Both in the
11 Boones as well as in the Baltimore patient, you see the
12 same clinical symptoms. You see a disruption of
13 coagulation. You see disruption of the cytokine
14 release. And we think that the virus may interact with
15 receptors on endothelial cells or human cells to
16 achieve this effect.
17 **DR. JAY FISHMAN:** Do we have data though to
18 show that human endothelial cells are infected? Or
19 could it be only from the xenograft endothelial cells?
20 **DR. JOACHIM DENNER:** No. I think it may
21 interact with human endothelial cells, but not infect

1 but interact. Viral protein interact with endothelial
2 cells by certain receptors and induce these infect.
3 This is one proposition at the moment. We have no
4 evidence that it can infect human cells.
5 And concerning all other viruses, our
6 knowledge is very limited. Some viruses, for example,
7 the pseudorabies virus, it can infect humans and can
8 even be harmful. But this virus is eliminated from
9 pigs, so we do not need to bother about this virus.
10 But many viruses are not well studied. But we never
11 saw their transmission, and we never saw clinical
12 symptoms.
13 **DR. JAY FISHMAN:** Thank you.
14 **DR. LISA BUTTERFIELD:** Thank you. It's a
15 complicated setting. Let's move to a question from Dr.
16 Wu and then Professor Fox next.
17 **DR. JOSEPH WU:** Yes. That was a great
18 presentation. And I think, as you know, there are more
19 and more of these zoonotic viruses that get spread.
20 One example is the SARS-CoV-2 virus. And I wonder, in
21 the future if we have these in xenotransplant, would

1 you also have to monitor the family members who are
2 living with the patient?
3 And the second question I have is, besides the
4 routine viruses that you study, are there studies in
5 which investigators heavily immunosuppress the pig and
6 see if any type of additional viruses pop up in a
7 heavily immunosuppressed pig model assuming that what
8 happens to the patient is a cyanotic organ transplant
9 and is heavily immunosuppressed. So, two questions.
10 **DR. JOACHIM DENNER:** Thank you very much.
11 These are two very important question. I mean, I think
12 that if you don't have a virus in the pig, you do not
13 need to look at the recipient. If you don't have the
14 virus in the recipient, you do not need check his wife
15 and his children. So, I think if you have a
16 transmission then you should be careful whether he can
17 transmit it to relatives but only in this case.
18 And the second question is also very
19 interesting. And I'm not aware of studies where
20 heavily immunosuppressed pigs have been studied. And
21 there are some reports that pigs which have PCMV/PRV

1 that this virus of course then is activated and is
2 replicating fast. But most of the other virus are not
3 studied, especially not so-called unknown viruses.
4 **DR. JOSEPH WU:** Got it. Thank you.
5 **DR. LISA BUTTERFIELD:** Thank you. And,
6 Professor Fox, your question.
7 **DR. BERNARD FOX:** Yes. Yeah, again, thank you
8 for a wonderful talk. On one of the slides that you
9 were discussing, you were talking about the
10 susceptibility of non-human primates to the PERV virus.
11 And on the slide, it says the "receptor does not fit
12 well." So, I guess you understand or you know what
13 that virus receptor is for the PERV in the cynomolgus
14 monkey. But do you know what that receptor is in
15 human? Is it the same receptor? Do we know if the
16 virus fits well in that human receptor, or does it not
17 express the receptor?
18 **DR. JOACHIM DENNER:** Yes. The receptor for
19 PERV-E at least is well known. It is known in humans,
20 and it is known in non-human primates if they are
21 related. And the problem is that you can infect non-

1 human primate cells, but the virus does not replicate
2 as well as in human cells. So you get less virus out
3 than you put in.

4 **DR. BERNARD FOX:** Okay.

5 **DR. JOACHIM DENNER:** And, therefore, these
6 non-human primate models are not a good model to say it
7 is safe.

8 **DR. BERNARD FOX:** So I guess that was my point
9 with the clinical data that you presented then in terms
10 of the studies where they were negative, but they were
11 all going into the cynomolgus monkeys as the transplant
12 so you got a negative result there. It may not inform
13 as well as in the clinical study, correct, in a human?

14 **DR. JOACHIM DENNER:** Correct. Right. But
15 unfortunately, at the moment, we do not have
16 experimental tools to investigate which risk they both
17 pose. At least we have to wait for the first
18 transplantation in humans which live long enough to see
19 whether it will be transmitted or not.

20 **DR. BERNARD FOX:** Thank you, very much.

21 **DR. LISA BUTTERFIELD:** All right. Now, we'll

1 hear from Dr. Kimmel followed by Dr. Auchincloss.

2 **DR. PAUL KIMMEL:** Thank you, Dr. Denner, for

3 your comprehensive talk. I wanted to ask you a

4 question about your elimination program. And I was a

5 little confused. I understood the rationale for using

6 a pig that is completely clear of the evaluated

7 viruses. Why would one use a low virus load pig and go

8 through vaccines and treatments if you are trying to

9 maximize human safety? Wouldn't it be more rational

10 and efficient to just take the absolutely negative,

11 clean pigs?

12 **DR. JOACHIM DENNER:** Yes. You are, of course,

13 absolutely right. But in many cases, we don't have

14 absolutely clean pigs. I mean, you see in the case of

15 PCMV/PRV nobody has such clean pigs. And we all had to

16 start with infected ones in our experiments.

17 **DR. PAUL KIMMEL:** I see. No, now, that puts

18 it into perspective. What is the percent of clean pigs

19 to sort of evaluate the efficiency of this sort of

20 development manufacturing process?

21 **DR. JOACHIM DENNER:** I mean, this depends on

1 the virus. If you look at PCV, you nearly have no
2 clean pigs. Porcine endogenous retrovirus, you also
3 don't have clean pigs. But, for example, with
4 circovirus, you have enough clean pigs to operate with.
5 **DR. PAUL KIMMEL:** Thank you very much.
6 **DR. LISA BUTTERFIELD:** Thank you. And, Dr.
7 Auchincloss, please.
8 **DR. HUGH AUCHINCLOSS:** I want to pursue the
9 same line of questioning. Is it your view that any
10 clinical xenotransplantation in the future should come
11 from a pig that is part of a herd that is specific
12 pathogen free? And if so, which viruses need to be
13 proven to be absent?
14 **DR. JOACHIM DENNER:** This is a very difficult
15 question. At least the known zoonotic viruses --
16 hepatitis E, PCV -- they should be absent. Concerning
17 all other viruses, we have to continue our
18 investigations and have to find whether they pose a
19 risk or not. At the moment, there are no reports that
20 other viruses can harm recipients. But we have at
21 least these two viruses which would be eliminated.

1 **DR. HUGH AUCHINCLOSS:** Thank you.

2 **DR. LISA BUTTERFIELD:** Terrific. Well, thank
3 you, again, Professor Denner. Oh, do we have one more?
4 So I'm seeing hands going up and down. Because we've
5 got a few more minutes before we start the discussion.
6 So, Dr. Zeiss, another follow-up question and then Paul
7 Conway after that.

8 **DR. CAROLINE ZEISS:** Hi, Dr. Denner. I wonder
9 if you could comment on the risk of
10 encephalomyocarditis transmission. You know, it's a
11 virus that resides in rodents, it does infect pig
12 hearts, and it has been shown to infect human
13 myocardial cells.

14 **DR. JOACHIM DENNER:** At least we didn't study
15 this. We didn't study this virus in donor pigs. We
16 didn't study transmission. So, you see, there are some
17 viruses which have to be analyzed.

18 **DR. CAROLINE ZEISS:** Thank you.

19 **DR. LISA BUTTERFIELD:** And, Mr. Conway, did
20 you have a final question? Your hand went down. Yes.
21 Yes, Mr. Conway.

1 **MR. PAUL CONWAY:** Thank you, very much. And
2 sorry for the confusion on the hand. Doctor, I want
3 you to step back for a second. I'm a kidney patient,
4 and there are many patients across the United States
5 and across the world that are paying attention to this
6 issue.
7 So, based on your expertise and what you see,
8 if you were sitting in front of or standing in front of
9 an audience of patients and families who are waiting on
10 an organ donation list today and you think back over
11 the past five to ten years, what is your level of
12 optimism about the safety and future of
13 xenotransplantation for patients? What would your
14 words be to that audience -- ones of optimism, guarded
15 caution, or pure caution? Just out of curiosity.
16 Thank you.
17 **DR. JOACHIM DENNER:** Thank you for your
18 question. I mean, when we are able to use sensitive
19 methods and when we are able to test correctly -- and I
20 will in my second talk give some better details. When
21 we can do this, I'm sure that we can make it safe. And

1 when we consider that the patient lived two months,
2 this is actually a great success. Because at first,
3 allotransplantations involved lived 18 days. The first
4 allotransplantation heart in Germany lived 24 hours,
5 and now we have two months. And without the virus,
6 maybe he would have lived longer.
7 **MR. PAUL CONWAY:** Thank you very much, sir.
8 **DR. LISA BUTTERFIELD:** Terrific. Well,
9 Professor Denner, that concludes the discussion and
10 questions to you at this point. Thank you very much.
11 A lot of very important information to share with the
12 Committee.
13 **DR. JOACHIM DENNER:** Thank you.
14
15 **COMMITTEE DISCUSSION OF QUESTION #1**
16
17 **DR. LISA BUTTERFIELD:** So, now we're going to
18 move to discussion of Question 1 for the Committee.
19 So, I think we'll have Question 1 come up. So -- and
20 this directly follows on to our discussion.
21 So, the question: pigs can harbor endogenous

1 viruses that may impact the health of transplanted
2 tissues or organs or impart infectious disease risk to
3 the recipient and their close contacts. PCV 3, PERV,
4 and PCMV have been identified as viruses that may
5 impact organ function after transplantation or be
6 transmitted to recipients of xenotransplantation
7 products, their contacts, and the public.
8 So, please discuss the following. We have
9 some sub-questions, and then I'll call on our two
10 discussants. Was there a next slide? Ah, and this is
11 all much too small for me to see. So, I'm going to my
12 page here. So, we've got to discuss sensitive
13 detection systems available for detection of infectious
14 agents in pigs. Which methods should be used
15 orthogonally?
16 PCV 3 transmission from donor pigs to baboons
17 has been reported. Please discuss the potential for
18 PCV 3 xenozoonotic infections in humans.
19 Again, PCV 3-infected pigs have been reported
20 to exhibit cardiac and multisystem inflammation. What
21 is the impact of PCV 3 on transplanted organs?

1 And then, the three subtypes of PERV (A, B,
2 and C) and the recombinant have been found in various
3 breeds of pigs. Which subtypes present the greatest
4 risk, and how can that risk be eliminated?
5 And finally, discuss any known or emerging
6 viruses that should be considered in the context of
7 human xenotransplantation.
8 So, we have five subtopics to discuss. And
9 so, first, I'll call on our two discussants, and then
10 I'd like to hear from the permanent and temporary
11 committee members. So, first" discussant is Dr.
12 Fishman.
13 **DR. JAY FISHMAN:** Thanks very much. And
14 thanks for inviting me to discuss this important topic.
15 I'd like to go back to the first slide, if I could, to
16 discuss a little terminology. Because the term
17 "endogenous viruses" is a little bit misleading in the
18 sense that the only endogenous virus we're talking
19 about is the porcine endogenous retrovirus, which is a
20 provirus, which is found in the genome of animals, be
21 it human, pig, or anywhere else.

1 So that we do have endogenous viruses. Humans
2 have them, and the pig has had that particular virus.
3 And we'll talk more about PERV in a second. The other
4 viruses -- the herpes viruses -- would be considered
5 latent viruses -- viruses that are normally controlled
6 by the immune system but are present for the lifetime
7 of the donor animal or any individual that becomes
8 infected.
9 So, I would distinguish first just for the
10 sake of discussion between the true endogenous viruses
11 and the exogenous viruses, which are infections that we
12 all might get. So, we might get herpes simplex, or we
13 might get zoster or something of that. And that stays
14 in our bodies forever. But those are latent viruses
15 that are generally controlled by the immune system.
16 The second aspect is the porcine circovirus 3
17 has not been shown to infect human cells. Porcine
18 cytomegalovirus has not been shown to infect human
19 cells. What they have been shown to do is increase in
20 viral load in detected virus during the course of a
21 xenotransplant experiment. Now that's very different.

1 What is implied is that the xenograft is at
2 least infected. And, therefore, if it was excluded
3 from the donor herd, that it wouldn't cause a problem
4 in the recipient. And, therefore, porcine circovirus,
5 porcine cytomegalovirus could potentially be excluded
6 from a herd and then not cause problems in the future.
7 But in the current situation, they may cause
8 infection of the xenograft, and they may rise in level
9 during the course of time. But in fact, we don't know
10 if any human cells have become infected.
11 So, just with that as background then to go --
12 the detection systems in the first question -- A in the
13 next slide -- become very important. So that a
14 detection system which detects prior exposure, say, to
15 porcine cytomegalovirus, we use comparable assays in
16 human allotransplantation, and we use serology --
17 antibody-based tests. And what those tests say to us
18 is that the body has had an immune response previously
19 to a virus and that that virus is still sitting in the
20 body somewhere.
21 And, therefore, that is important because it

1 means it can be reactivated in a graft in the setting
2 of immune suppression required immunologically. So,
3 that's serologic testing. So it's an indicator of past
4 infection and a very useful but less sensitive kind of
5 assay.
6 The subsequent kinds of testing look at the
7 presence of the virus, and there are a lot of different
8 tests for that. You can do sequencing, which is a
9 little more complicated. We do a polymerase chain
10 reaction or nucleic acid test -- we call it the NAT
11 test -- and that will tell us whether or not there's
12 circulating virus. But it still doesn't tell us
13 whether or not human cells are infected. It only tells
14 us that virus is present in circulation.
15 So that if you see a rising nucleic acid test
16 quantitation, it may suggest that infection has
17 progressed, but it doesn't tell you where it is. And
18 you need some form of histology, some pathology, some
19 electron microscopy, potentially immune fluorescence
20 microscopy, but some mechanism that ties that virus to
21 the cells.

1 The complicating feature is that if you have a
2 organ, they may lose -- they may shed cells. They may
3 shed virus. So, the virus that we see in circulation
4 may come from human cells, or it may just come from the
5 xenograft itself. So, the sensitive detection system
6 should depend on the virus that you're trying to
7 detect.
8 PCV B and C on the current slide, therefore,
9 may appear to affect the baboon, but all we know is
10 that it at least affects the transplanted organ. From
11 that site, we may see cardiac or systemic inflammation
12 which may affect the recipient systemically. But we
13 don't know whether or not human organs are affected or
14 it's simply coming again from the pig heart or kidney
15 or other organ.
16 Let me move to the porcine endogenous
17 retrovirus, and then I'll make one other comment. The
18 three subtypes of PERV and PERV A/C recombinants have
19 been found in various breeds of pigs. The subtypes
20 that present the greatest risk, the receptors in humans
21 have been cloned for PERV A and there are receptors

1 from PERV B. So, potentially PERV A and B can infect
2 human cells; PERV C cannot. However, if you take a
3 piece of PERV A and a piece of PERV C and put them
4 together, the PERV A/C recombinants, they potentially
5 could infect human cells.
6 It has never been shown to infect normal human
7 cells. So all the studies have been done with
8 transformed cells, which have defective self-protecting
9 mechanisms. Therefore, we don't know. And the
10 likelihood is that it's possible, but infection of
11 humans has never been demonstrated for any of the PERV
12 species.
13 So, in terms of which subtypes present the
14 greatest risk, we're talking about a long-term
15 experiment in which a potential exposure to an
16 endogenous retrovirus may occur if it's not eliminated
17 from the donor herd. And I think we don't know that.
18 But what we do know is that with multiple exposures,
19 all of the experiments we've done, infection of normal
20 human cells by PERV has never been seen.
21 And then in terms of other known or emerging

1 viruses, Dr. Denner talked about hepatitis E, which is
2 a known human pathogen. We have swine influenza, which
3 as we all remember can infect human lung tissue. But
4 there are no other viruses that are of immediate
5 concern.
6 However, there are some viruses that are
7 similar to viruses that infect humans -- I'd use
8 adenovirus as an example, which potentially could
9 infect humans -- but we don't know of any such
10 infections. And, therefore, the strategy I think that
11 is worth taking is looking at the pathogens that affect
12 immunosuppressed human hosts and asking the question,
13 are there comparable pathogens in swine and eliminating
14 those as potential pathogens of immunosuppressed human
15 hosts.
16 But I would emphasize, we don't have any data
17 that any of these organisms should be considered in the
18 context of human xenotransplantation.
19 So, let me pause there and see if I have
20 adequately confused everybody, or whether or not any of
21 what I just said makes any sense.

1 **DR. LISA BUTTERFIELD:** Thank you very much,
2 Dr. Fishman. I really appreciate your perspective. I
3 guess one question I'll ask right off is, it sounds
4 like amongst these unknowns are some questions we might
5 address -- and the sponsors of these therapies might
6 address -- experimentally in terms of in vitro culture
7 even to determine whether some of these viruses can
8 infect human cells. Would that make sense to you?
9 **DR. JAY FISHMAN:** Yes. And many of those
10 experiments have been done. Porcine cytomegalovirus
11 does not easily -- you can overwhelm the system but
12 does not easily infect human cells. Porcine endogenous
13 retrovirus does not infect normal human cells. And
14 that's been studied. I do not believe there are any
15 data to show that PCV 3 infects normal human cells.
16 And I would throw into this that coronaviruses are
17 pandemic pathogens. There are swine coronaviruses, and
18 they don't infect human cells. And human coronaviruses
19 do not appear, in some limited studies, to infect pigs.
20 So then, the viruses that we might consider to
21 be of greatest concern have actually been studied. The

1 other possibility is, can we use the preclinical, non-
2 human primate model? And the answer is yes to a
3 degree. But as you heard from Dr. Denner, the
4 pathogens that infect humans may not infect baboons
5 very well, and PERV is a perfect example. And so,
6 baboon studies may not be informative.
7 So, as you say, studies in vitro on human
8 cells are maybe informative. But the issue is are
9 those comparable in the sense because the human host is
10 immunosuppressed and there's surgical differences and
11 the patients are sick? So, it's not perfect, but I
12 think that there is some burden to suggest that common
13 pathogens have been looked at and have not been shown
14 to infect human cells. But certainly, we'd want to
15 look into recipients of xenograft to make sure by
16 specific assays or by non-specific assays that
17 infection has not occurred.
18 **DR. LISA BUTTERFIELD:** Thank you. So, let's
19 move to our second discussant, Dr. Basavaraju. And
20 then we'll open it up to the full Committee to discuss
21 Question 1 and the sub-questions.

1 **DR. SRIDHAR BASAVARAJU:** Okay. Thank you.
2 So, we have a long history and experience at CDC of
3 studying and investigating transmission events through
4 human organ transplantations so from human donors
5 obviously to the human recipients. The experience, we
6 don't have obviously of studying animal organs to human
7 recipients, of course. And I would agree with Dr.
8 Fishman's perspectives as well.
9 There are, I think, a few additional issues
10 that -- when we were discussing these questions prior
11 to this meeting internally at CDC with some of our own
12 health experts, the questions, I guess, that we think
13 remain unresolved and probably can only be identified
14 and answered in the real-life scenario as more of these
15 transplants are done is, if you have organs from any of
16 these animals and they are infected with some of the
17 viruses, whether it's PCV, PERV, or in the setting of -
18 - even if some of these have not been shown to affect
19 human cell lines, some of them have been shown to be
20 transmitted to baboons.
21 And the question really, I think, that we

1 can't -- it would all just be speculative at this point
2 is, if you put these into a very ill human who's very
3 heavily immunosuppressed, what would be the effect?
4 So, for example, even if you don't have transmission
5 per se to the human, the fact that this was in the
6 animal organ itself would not result in organ failure,
7 for example. And I think that that's not -- I think
8 it's -- from our perspective, that just seemed a little
9 bit speculative without additional data.
10 So, I think moving forward, what we would say
11 is that -- or what our input would be is that there
12 should definitely be testing for these pathogens in the
13 animals. And to the extent possible, that organs are
14 recovered from pathogen-free herds. And that there
15 should be standardized -- continuous follow-up of
16 recipients with standardized testing at some set
17 intervals, for example, for these pathogens.
18 As far as the emerging viruses or known
19 viruses that should be considered in the context of
20 human genome transplantation, we would certainly add
21 hepatitis E to that because that's something that's

1 been known and documented in pigs, of course. And when
2 we have looked at hepatitis E transmission from human
3 organs, the effect sometimes are -- there are some
4 morbidity involved with those.
5 **DR. LISA BUTTERFIELD:** So, thank you very
6 much. May I press you a little bit on the standardized
7 testing suggestion? Do you have any specifics? Do you
8 think there's a platform that can do it all? Or do we
9 need to adjust the platform for the virus we're testing
10 for? Would that include open-ended, adventitious virus
11 type of testing? What are your thoughts on the testing
12 and the frequency?
13 **DR. SRIDHAR BASAVARAJU:** Well, in terms of
14 frequency, I guess I'm not sure. I'd say more
15 frequently early on, you know, every few weeks probably
16 early on. And then, I guess, hopefully, these
17 recipients will survive longer. And with that I think
18 eventually I would say maybe every month for the first
19 year and then once or twice a year after that,
20 potentially, even if they're feeling well, for example.
21 I think that in terms of actual testing

1 platforms, I would probably have to defer to Dr.
2 Fishman and others about that. I know that there are -
3 - well, yeah, I think I probably would defer to some of
4 the other experts on that.
5 I do think that it would be important to have
6 sample archives from the donor animals as well as from
7 the recipients. That, I think, would be useful for
8 future studies, particularly if there are other
9 emerging pathogens that are subsequently identified. I
10 think it would be useful to be able to go back to see
11 if any of these were present in the animals prior to
12 organ recovery and the recipients after
13 transplantation.
14 **DR. LISA BUTTERFIELD:** All right. Thanks
15 again. So, let's move now, now that we've had our two
16 discussants to get the discussion rolling. I'm looking
17 for hands to hear from the other members of our group.
18 And so let's start with Dr. Palevsky, and then we'll
19 move to Dr. Ahsan.
20 **DR. PAUL PALEVSKY:** Sure. Thank you. So, I
21 am a novice when it comes to virology. But a couple

1 key questions, what do we know, if anything, about the
2 effect of the level of immunosuppression that a
3 recipient would need to have in xenotransplantation on
4 the virus in the donor animal? Have there been studies
5 done looking at, say, porcine CMV-infected animals that
6 get the level of immunosuppression for induction and
7 maintenance immunosuppression?
8 Since, from what I understand from what's been
9 said so far, while the virus may not infect human
10 cells, it can proliferate in the donor organ and,
11 therefore, result in early failure of the donor organ.
12 The second question that I would pose is, what
13 is the risk if there's co-infection of porcine CMV and
14 human CMV in the same recipient, so the organ carried
15 the virus and the recipient is positive for the virus
16 to get a recombinant virus that then could infect human
17 cells?
18 Or for one of the other viruses that we
19 haven't discussed such as a porcine adenovirus with a
20 human adenovirus co-infection, what are those risks?
21 **DR. LISA BUTTERFIELD:** All right. Well, so,

1 I'm just going to go in order, and, hopefully, someone
2 will weigh in to address your questions. Next is Dr.
3 Ahsan and then Dr. Fishman.
4 **DR. TABASSUM AHSAN:** Great. Thanks. You
5 know, I really don't understand the clinical side. So,
6 we've been talking a little bit about the likelihood of
7 infection. But what are our clinical management
8 schemes? So, maybe those that are in the
9 allotransplantation world have an understanding. If
10 there was to have the infection, what are the
11 implications to the recipient of those viral loads
12 either just in the infectivity or even the management
13 of the immune response when the transplant organ has an
14 increased viral load and the recipient's immune
15 response is burdened by that.
16 Do we have -- Dr. Fishman, would you be
17 someone who would have knowledge on the clinical
18 outcomes of what you would do for a patient that had
19 been infected?
20 **DR. LISA BUTTERFIELD:** All right. And Dr.
21 Fishman is next in our queue. So, we'll see if he can

1 address some of these questions that have now come up.

2 **DR. JAY FISHMAN:** Great questions only in the

3 fact that I've investigated most of those in the lab.

4 So, thank you very much for all those questions. I'll

5 go back.

6 The distinction I would make, which you've

7 heard -- which people have gotten quite well is

8 infection located in the xenograft versus systemic

9 infection. Porcine cytomegalovirus is a good example.

10 So, we showed in the baboon model that the

11 amount of infection due to PCMV went up with the

12 intensity of immune suppression. That's the same thing

13 we see in human transplants is that the level of viral

14 replication goes up with the intensity of immune

15 suppression. However, in the pig to primate model,

16 that infection stopped abruptly at the anastomosis.

17 So, in other words, if you had a vascular or ureteric

18 anastomosis it stayed in the pig tissue.

19 But there were systemic manifestations --

20 consumptive coagulopathy, platelet consumption,

21 clotting abnormalities, cytokine release and fevers,

1 and graft loss -- that were associated with PCMV even
2 though they didn’t infect the baboon host in that
3 setting. So, systemic effects for sure, detection of
4 virus in the bloodstream for sure, but the infection
5 stayed in and damaged the graft so, an important
6 infection.
7 Dr. Palevsky asked about co-infection. And we
8 actually studied our animals that had co-infection with
9 porcine cytomegalovirus and PERV and found there was no
10 interaction between those two viruses. But the
11 question is a good one because my own lab has studied
12 the impact of herpes viral infections on immune
13 responses. And you would expect that human CMV would
14 reduce the ability of the human host to fight off other
15 infections. And we’ve shown that.
16 However, we don’t know, since it doesn’t
17 infect human cells, that the same effect would occur
18 due to porcine cytomegalovirus. As Dr. Denner pointed
19 out, these viruses are different. So, in each
20 situation, we know that we have to look at the
21 individual virus. So, is co-infection important? Yes.

1 If human CMV is present in the human recipient, they
2 are going to be able to fight off other infections less
3 well.
4 Now, the question is what do we do about that?
5 And our own studies have shown that the drugs that we
6 use for human cytomegalovirus don't work as well in
7 normal drug levels against porcine CMV. So we don't
8 want that virus in our recipients because the drugs we
9 have don't treat it as well. They work all right for
10 prophylaxis, not very well for therapy. Conversely,
11 the drugs that we have for porcine endogenous
12 retrovirus are drugs that we have for HIV, and it
13 worked very well.
14 So we have very good drugs for PERV, but
15 there's no evidence of infection of human cells by
16 PERV. So, again, we're back in the situation where for
17 each virus we have to have a preventative or
18 therapeutic strategy. We don't have good ones for
19 PCMV, we don't have good ones for the porcine
20 circoviruses. You know now that we have some decent
21 antivirals for coronaviruses, but they don't cross

1 species.

2 So, we have to look at each potential pathogen

3 on its own and, again, with the concept that preventing

4 disease is easier than treating disease and that there

5 are plenty more studies left to do. As Dr. Butterfield

6 said, we can do some of those in vitro.

7 **DR. TABASSUM AHSAN:** Yeah. I mean, I guess

8 one question I have is, you know, this -- our

9 discussion is in isolation of any particular

10 application, right. And so, not knowing the -- it's

11 all about risk to benefit ratio. So, of course, it

12 would be ideal to have clean transplantation material.

13 But in the case where the urgency of the need outweighs

14 the risk of the infection, what I'm trying to

15 understand is the clinical implications of those

16 infection and not just whether or not that infection

17 would be present.

18 And in terms of the clinical implication, I

19 understand the isolation and the tax it might have on

20 the immune system of the recipient versus actual

21 transmission to the human cells. But what I don't

1 understand, because I don't have the expertise, is what
2 are the clinical options for managing those scenarios?
3 **DR. JAY FISHMAN:** So, if I could respond to
4 that, because the field of human-to-human
5 allotransplantation was changed by the availability of
6 drugs for hepatitis C and hepatitis B and for HIV,
7 therefore, we are able to use organs that we previously
8 couldn't use because we had no therapies and that
9 patients would become ill due to the viruses they were
10 carrying. So, the availability of therapeutics
11 broadens your possibilities. So, you put your finger
12 exactly on where the field has gone in the last five to
13 ten years in allotransplantation.
14 We don't have the same level of information
15 about all the potential pig pathogens. But because
16 humans are immunosuppressed for xenotransplantation as
17 would be for allotransplantation, we can't take the
18 risk of putting in pathogens that will replicate in the
19 human recipient in that setting. So, in the absence of
20 therapeutics, it's probably a risk we don't want to
21 take.

1 So, if you needed a heart, I could give you a
2 heart. And we do this routinely on individuals who are
3 carrying human CMV, human hepatitis C, hepatitis B,
4 because we have therapies, and the urgency outweighs
5 the risk. You would not necessarily want to take a
6 heart that was infected with HIV, even though we can
7 treat it, because it commits you to a lifetime of anti-
8 HIV therapy. So, there is an informed consent
9 component, although we're not dealing with ethics.
10 That's the piece of it.
11 So, the availability of diagnostics and
12 therapeutics is key in terms of whether or not the
13 risk-benefit equation that you referred to. And so,
14 for an individual, they might say, I'll take a liver or
15 a heart or lungs from a pig, and I'm not going to worry
16 about this. And another individual might say, I would
17 never do that. So, I don't think there's a single
18 right answer.
19 **DR. TABASSUM AHSAN:** Yeah. I mean, I guess
20 one of the elements -- not to take up too much time,
21 but one of the elements is it's great to think about

1 the consent aspect, but we also need to think about the
2 release aspect of whether these products are being
3 released to be used and whether we -- the stringency
4 with which we set that criteria. And we'll be talking
5 about that a little bit later in Question 3. So thank
6 you for your input. That was very helpful.
7 **DR. LISA BUTTERFIELD:** Great. Thank you both.
8 Next, we'll hear from Dr. Wu.
9 **DR. JOSEPH WU:** Yes. So I have a question for
10 Dr. Fishman or the experts on the in vitro testing.
11 Hypothetically, if you take a patient population, which
12 is quite heterogeneous, and if you have a hundred
13 people and expose them to some kind of pig virus,
14 perhaps 99 percent of them are not infected and only
15 one percent are infected for one reason or the other --
16 genetic variability, susceptibility and so forth.
17 So, my question is, on the in vitro assays
18 that you are doing, it shows that the pig virus does
19 not affect human cells. I assume most of it is based
20 on one or two cell lines. And how confident are you to
21 make the call that if you don't see an infection in one

1 or two cell lines rather than say a hundred different
2 patients in a cell line -- to make the call that, oh
3 yeah, pig virus does not affect the human cells?
4 So it may be just that the analogy I gave with
5 the human population with a hundred people that get
6 exposed, only one percent get a bad response from the
7 pig virus.
8 **DR. LISA BUTTERFIELD:** And I see a hand from
9 Professor Denner. Would you like to respond?
10 **DR. JOACHIM DENNER:** To answer your question,
11 we do not know exactly whether PCMV/PRV can infect
12 human or baboon cells. Maybe that there are some stem
13 cells in the organism which are infected. We do not
14 know. But I think it's also not important. Important
15 is that we see a disease in the human. In the
16 Baltimore patient, we see disease in our baboons, and
17 we should do everything to prevent this disease. And
18 this disease, we can prevent eliminating the virus from
19 the pig.
20 **DR. LISA BUTTERFIELD:** Dr. Wu, did that answer
21 your question? I can't hear you, Dr. Wu.

1 **DR. JOSEPH WU:** Yeah.

2 **MR. MICHAEL KAWCZYNSKI:** Unmute your phone.

3 There you go.

4 **DR. LISA BUTTERFIELD:** Sorry. So that did

5 answer your question?

6 **DR. JOSEPH WU:** It did.

7 **DR. LISA BUTTERFIELD:** Okay. Thank you.

8 Thank you both. All right. So, I'm looking for

9 additional hands from people with other questions or

10 thoughts on addressing these five sub-questions. And

11 so, next, I'm going to move to Marshall and then Hugh,

12 please.

13 **DR. MARSHALL BLOOM:** I'd like to -- the

14 presentation was absolutely terrific. And I thought

15 the comments so far have really been superb too.

16 I worked for many years in a lab where there

17 was a guy working on endogenous mirroring retroviruses.

18 And I've tried to suppress as much of that as I was

19 able. But a few things still occur to me is that, in

20 the mouse system, you have full-length endogenous

21 viruses and then you have other pieces of endogenous --

1 remnants of endogenous retroviruses.

2 And my recollection is, is that under some

3 circumstances those could recombine to form I think --

4 I can't remember the specific term for that. So one

5 question I'd be curious about is, would something like

6 that be a possibility in the pig setting? Are there

7 both full length -- so, you have A, B, C and the A/C

8 recombinants, but are there also smaller fragments of

9 endogenous retroviruses which might recombine to come

10 up with a virus which might cause a problem? That was

11 one question.

12 The other question which may be easier is that

13 Dr. Denner was talking about -- he started off in his

14 earlier slides with about five or six different kinds

15 of pigs. And then they focused in on a particular kind

16 of pig which I think was the Göttingen minipigs. And

17 we earlier heard that anything in the United States

18 would have to be from a domestic pig. So, in terms of

19 the -- and the viruses which to me are really of the

20 most concern would be these endogenous retroviruses.

21 How different is the endogenous retroviral

1 virome in different species of pigs around the world?
2 Thanks.
3 **DR. LISA BUTTERFIELD:** Okay. Why don't I ask
4 Professor Denner to respond?
5 **DR. MARSHALL BLOOM:** Yeah.
6 **DR. JOACHIM DENNER:** Concerning your first
7 question, of course, there are recombinations in the
8 pigs. For example, the PERV A/C recombination takes
9 place in the living pig. So, we have different copies
10 of PERV in different organs which indicate that in the
11 pig, the virus is active. It replicates in the pig,
12 and it is able to recombine into PERV A/C. The PERV
13 A/C was never found in the germ line of the pig, but it
14 is often found in different somatic cells in different
15 organs.
16 Concerning the relationship between the
17 porcine endogenous retrovirus and the human endogenous
18 retrovirus, which are all in us, I can say that there
19 is no close relationship that recombination would be
20 possible.
21 **DR. MARSHALL BLOOM:** Okay. And then, to the

1 second question since you're probably the -- you and
2 Dr. Fishman would be the ones to know, how equivalent
3 is the retroviral load and characteristics from one
4 strain of pig to another?
5 **DR. JOACHIM DENNER:** Oh. Yes, we performed an
6 analysis of the copies number of PERV in different
7 pigs. And it changes from 20 to 60. And it is
8 different in different pig breeds. But as a
9 virologist, I have to say, it's not important how many
10 copies you have in the pig. Important is how many
11 viruses can replicate and can infect human cells. And
12 this is why we didn't see in German Landrace pigs such
13 PERV A/C recombinants, but we saw them in minipigs
14 because they are more in-bred.
15 And obviously, the number of replication-
16 competent provirus in the minipigs is higher. And
17 especially of some PERV C which are necessary for the
18 recombination between PERV A and PERV C. Therefore, in
19 minipigs, we more often see PERV A/C recombinants. And
20 as I said, in one case, we even found a virus which was
21 released from the Göttingen minipig and was able to

1 infect human cells but again transformed human cells,
2 293 cells, not normal cells.
3 **DR. MARSHALL BLOOM:** Thank you. And, you
4 know, there's a couple of synapses connected here. And
5 one other virus, which can be fairly cryptic but which
6 can integrate under some circumstances, are the adeno-
7 associated viruses. And I'm not a hundred percent
8 certain, but I believe there are pig adeno-associated
9 viruses. Is that something that you -- I mean, your
10 studies have been amazingly comprehensive. I'm just
11 curious if you have ever looked for adeno-associated
12 viruses?
13 **DR. JOACHIM DENNER:** No. No. I mean, there
14 are so many viruses in pigs. And we concentrated on
15 the potentially zoonotic.
16 **DR. MARSHALL BLOOM:** Okay. Thanks, very much.
17 **DR. LISA BUTTERFIELD:** Great. Thank you both.
18 We're going to go to Dr. Auchincloss, and then if Dr.
19 Fishman still wants to weigh in afterwards there.
20 Thank you. Do we have Dr. Auchincloss and his question
21 now?

1 **DR. HUGH AUCHINCLOSS:** Okay, here we go. I'm
2 actually going to pose my earlier question to Dr.
3 Fishman, which is, what is the minimum standard of
4 cleanliness would you impose on future xenotransplants
5 by the FDA? Seems to me guaranteeing the absence of
6 porcine CMV is a no-brainer, and I would say the same
7 about PCV 3. But I don't know that that same standard
8 would apply to PERV at this point. Do you feel we need
9 to prove inactivated PERV, Jay?
10 **DR. LISA BUTTERFIELD:** So do we have Dr.
11 Fishman to respond to this?
12 **DR. JAY FISHMAN:** Here we go. Made it.
13 Exactly the right question, Hugh. I think the -- so
14 there's been distinctions drawn between PERV A and B
15 and PERV C and that's because of the in vitro
16 phenomenon of accelerated infection of the A/C
17 recombinant. It's reasonable, but in fact, it may not
18 speak to the real issue which is that the human
19 receptors are for PERV A that have been cloned and PERV
20 C can also infect human cells.
21 And therefore, I don't expect any symptomatic

1 infections due to PERV A, B, or C early after
2 transplantation. So, I think those are not the
3 concerns. The concern is -- gets back to the question
4 that was just asked which was, do I expect recombinant
5 events to occur later? And I have no way of knowing
6 that. But in the absence of data to suggest that PERV
7 A, B, or A/C can infect normal human cells, I don't
8 think we need to exclude them.
9 I think though the other question that was
10 asked just recently was, have we tried enough different
11 cell lines? And the answer is possibly not. But we've
12 used a lot of cell line. And Erickson, et. al.,
13 published a huge number of cell lines that they tried
14 to infect with PERV and were unable to infect any
15 normal human cells with porcine endogenous retrovirus.
16 So, would I feel better if there were no
17 copies? Yes. Do I feel that's an absolute criterion?
18 I would say no. And I would say I would differentiate
19 between the goal of this, which is providing organs for
20 life-saving transplant which applies to hearts, lungs,
21 and livers, and maybe we're going to have slightly

1 different criteria for kidneys. But that's my bias.

2 **DR. HUGH AUCHINCLOSS:** And what about PCMV and

3 PCV 3, should those be absent?

4 **DR. JAY FISHMAN:** So, PCMV I think should be

5 excluded because it will only infect the pig organ but

6 likely to stir up systemic inflammation and consumptive

7 coagulopathy. So, PCMV I would get rid of. Thus far,

8 we see only data that suggests that PCV 3 can infect

9 the graft but similarly seems to cause some

10 inflammation from within the graft. So, again,

11 reasonable to exclude those two.

12 PLHV doesn't infect human cells as best we can

13 say so, easy to exclude but not necessary. So, those

14 are the main actors.

15 I think then I would breed pigs that lack

16 other pathogens that are known to infect

17 immunosuppressed human hosts. Toxoplasmosis would be

18 an example of a parasite that infects pigs and infects

19 humans. So, you don't want that. So, that's how I

20 constructed my theoretical list of exclusion. But what

21 you're saying, Hugh, is very reasonable.

1 **DR. HUGH AUCHINCLOSS:** Thanks. That's
2 perfect.
3 **DR. LISA BUTTERFIELD:** All right. Thank you
4 very much for those specifics, Dr. Fishman. All right.
5 So, we've had a lot of great discussion. We've had
6 some specific recommendations. I'm not seeing any
7 other hands. So, perhaps I'll try to circle back and
8 sum up some of the points that have been raised and
9 then save a few minutes at the end in case there are
10 some other thoughts.
11 So, to all of these questions about the
12 endogenous viruses or non-endogenous viruses that we've
13 been discussing in pigs, there's a lot of testing that
14 could be done. There's some recommendations for
15 specific tests that have to be designed for specific
16 viruses, as well as considering non-specific
17 adventitious virus assays to look for the things that
18 are not easily seen. But there seems to be no one
19 platform that can attend to everything.
20 Staged testing in the setting of patients is
21 one possible model that if the donor of the organ is

1 positive for a virus, then to watch the patient for any
2 suggestion of disease. If the patient shows disease,
3 only then would one look to family members and more
4 broad testing.
5 There's been a lot of discussion about
6 possible recombination of viruses which are the viruses
7 that are more concerning for the human patient.
8 Certainly, the hepatitis C, swine flu, those can be
9 tested for and avoided, porcine CMV, which may or may
10 not cause direct disease, but there's evidence for
11 inflammation and coagulopathies from that that could be
12 bred out in pigs.
13 And so, while there's an opportunity to treat
14 and vaccinate, there's also an opportunity to breed
15 only those animals testing negative for these and have
16 those as the source of the organs. A lot of these
17 viruses have been tested in vitro, tested in patients,
18 and found to not infect normal human cells. Perhaps
19 only in vitro and transformed cells are only with high
20 concentrations of virus which reduces concern about
21 many of them.

1 And to test five PCR, one tests only for
2 replication of those viruses serologically for
3 exposure. So, in viruses that are not known to infect
4 human cells, these might not need to be done. There's
5 other considerations, of course, about the immune-
6 suppressed patient, which are not able to as easily
7 clear viruses as they might be able to. And so,
8 toxoplasmosis has been mentioned as something else that
9 could be tested for and eliminated, which would be a
10 particular concern in immune-suppressed patients.
11 But that being said, there are still many
12 unknowns and that some of these studies can only be
13 done in a clinical setting in human patients due to
14 limitations in baboons and some of the other animal
15 models that have been tested.
16 So, those were some of the highlights for me.
17 We had some specific recommendations about the exact
18 viruses that are more concerning and less concerning,
19 the need for standardized testing, and a suggestion
20 that perhaps up to weekly or biweekly testing early
21 after transplant followed by months and staging that as

1 the patient continues to survive with less testing
2 being needed over time at this stage of the field.
3 So, that is what I heard. So, any additional
4 comments of things that should be highlighted in the
5 summary? And I've got a couple -- I've got two Pauls
6 with their hands raised. The second is Paul Conway and
7 the first Paul, let's go to you whose last name I
8 cannot see.
9 **DR. PAUL KIMMEL:** Hi. It's Paul Kimmel.
10 Thank you for the summary. I think it was terrific.
11 I'm just interested -- and again, I'm not a virologist
12 or an infectious disease physician. We've talked a lot
13 about, does it infect human cells? And we know from
14 single-cell RNA experiments, single-cell nucleic
15 experiments, that there's a huge number of and
16 different kinds of cells in humans. Are we really okay
17 in producing any kind of document and saying it doesn't
18 infect human cells? Or shall we confine ourselves to
19 say it doesn't infect human cells that have been tested
20 on cell lines, et cetera?
21 **DR. LISA BUTTERFIELD:** I don't know if one of

1 our regulatory colleagues would want to weigh in on
2 this or perhaps let's move to first Paul Conway and --
3 oh, and now Dr. Denner.
4 **DR. JOACHIM DENNER:** As I said, we do not know
5 really whether it can infect human cells. At least the
6 cell lines which were tested over in my laboratory, we
7 were unable to infect. But there may be some stem
8 cells also in the organism which can easily be
9 infected. But I think it's more important to stress
10 that we should avoid the disease induced by PCMV/PRV in
11 the human patient and in the baboons.
12 This is important as infection is only a
13 secondary question. Because we can easily suggest that
14 the viral proteins can interact with human endothelial
15 cells and with human immune cells to induce these
16 changes in cytokine release and in coagulation without
17 infecting these cells.
18 **DR. PAUL KIMMEL:** Thank you. Yeah. I think
19 we just probably have to be circumspect in talking
20 about cells investigated or some kind of delineation.
21 So we don't end up having to say we over spoke ten

1 years later, you know.

2 **DR. JOACHIM DENNER:** Okay. Thank you.

3 **DR. LISA BUTTERFIELD:** All right. Thank you.

4 And, Paul Conway, did you have another comment still?

5 **MR. PAUL CONWAY:** Yeah. Just two quick

6 points. Thank you very much. Thank you, Dr.

7 Butterfield. Just two quick points. First, I think

8 the expert testimony and the Q&A and back and forth

9 here has highlighted a point that I had gone to

10 initially which is the importance of herds from known

11 origin. And I think that's going to be particularly

12 important for sponsors in the integrity of what we're

13 looking at in terms of where animals are from and the

14 history of them and how closely the facilities and the

15 process is monitored, especially for both patients and

16 for science.

17 The second point that I'd like to highlight

18 here is there's been a conversation about patients and

19 families and the risks posed to them. And I would say

20 that this is prime territory not only for transparency

21 in disclosure and consent but also something for FDA to

1 consider for mining and collecting patient and family
2 insight data so that the process is informed by
3 patients and families throughout as we move forward on
4 this. But very good discussion. Thank you.
5 **DR. LISA BUTTERFIELD:** Thank you, very much.
6 All right. Then before we close out this part of the
7 discussion for Question 1, I'll ask Dr. Bryan or other
8 colleagues from FDA if they have anything else they
9 would like to add before we close this out.
10 **DR. WILSON BRYAN:** No. Thank you, Dr.
11 Butterfield. No. I really appreciate the excellent
12 discussion. I think it has really been very helpful to
13 us. And it's set a high bar actually for the rest of
14 this meeting.
15 I will address a couple of questions from Dr.
16 Kimmel. I certainly think we want to endorse the basic
17 principle of, when we communicate, we need to specify
18 the limitations of our knowledge.
19 And to Dr. Conway, the importance of staying
20 in touch with patients and families and we have a
21 variety of initiatives at the FDA, particularly around

1 kidney replacement that are focused on understanding
2 the perspectives of patients and families.
3 **DR. LISA BUTTERFIELD:** Thank you so much, Dr.
4 Bryan. So, with that, I'd like to close out discussion
5 of Question 1. We have a lunch break. And the Open
6 Public Hearing we will keep on time. And so, that will
7 begin at 10:15 here in San Francisco or 1:15 for those
8 on the east coast of the U.S. And I will see you back
9 then.
10 **MR. MICHAEL KAWCZYNSKI:** All right. So let me
11 get up our timer here before we go. And that is -- how
12 long is our break? We have a 30-minute break. All
13 righty. So, see you all back in 30 minutes. Studio,
14 please kill the feed.
15
16 **[LUNCH BREAK]**
17
18 **OPEN PUBLIC HEARING**
19
20 **MR. MICHAEL KAWCZYNSKI:** Okay and welcome back
21 to our 73rd meeting of the Cellular Tissue, and Gene

1 Therapy Advisory Committee meeting. Thank you for
2 bearing with us as we were on break. I'm going to hand
3 this meeting off to our chair, Dr. Butterfield, as we
4 start our OPH session. Dr. Butterfield, take it away.
5 **DR. LISA BUTTERFIELD:** Terrific. Thank you,
6 Michael. Welcome back, everyone, and welcome to the
7 Open Public Hearing session.
8 Please note that both the Food and Drug
9 Administration, FDA, and the public believe in a
10 transparent process for information gathering and
11 decision-making. To ensure such transparency at the
12 Open Public Hearing session of the Advisory Committee
13 meeting, FDA believes that it is important to
14 understand the context of an individual's presentation.
15 For this reason, FDA encourages you, the Open Public
16 Hearing speaker, at the beginning of your oral
17 statement to advise the Committee of any financial
18 interests relevant to this meeting such as a financial
19 relationship with any company or group that may be
20 affected by the topic of this meeting.
21 Likewise, FDA encourages you at the beginning

1 of your statement to advise the Committee if you do not
2 have any such financial relationships. If you choose
3 not to address this issue of financial relationships at
4 the beginning of your statement, it will not preclude
5 you from speaking.

6 And that being read, I'd like to turn this
7 over to Christina for the Open Public Hearing session.

8 **MS. CHRISTINA VERT:** Thank you, Dr.
9 Butterfield. Before I begin calling the registered
10 speakers, I would like to add the following guidance.
11 FDA encourages participation from all public
12 stakeholders in its decision-making processes. Every
13 advisory committee meeting includes an Open Public
14 Hearing session during which interested persons may
15 present relevant information or views.

16 Participants during the Open Public Hearing
17 session are not FDA employees or members of this
18 Advisory Committee. FDA recognizes that the speakers
19 may present a range of viewpoints. The statements made
20 during the Open Public Hearing session reflect the
21 viewpoints of the individual speakers or their

1 organization and are not meant to indicate Agency
2 agreement with the statements made.
3 And now I will go ahead and introduce the
4 first speaker, which is Dr. Allan Kirk.
5 **DR. ALLAN KIRK:** Thank you very much. I am
6 assuming that my title slide is showing.
7 **MS. CHRISTINA VERT:** Yes. Go ahead.
8 **DR. ALLAN KIRK:** My colleagues and I would
9 like to thank the FDA for the privilege of addressing
10 the Committee today. I have no specific financial
11 conflicts. I have done research with organs supplied
12 by eGenesis and Revivacor. Next slide, please.
13 I'm speaking on behalf of the American Society
14 of Transplantation and the American Society of
15 Transplant Surgeons, who have chartered a
16 xenotransplant advisory panel comprised of leaders in
17 the xenotransplantation science, surgery, medicine,
18 infectious diseases, ethics, and administration along
19 with representatives from academia, industry, and
20 federal agencies, including national and international
21 individuals all assembled to provide broad insight and

1 knowledge in support of the safe and rational
2 development of clinical xenotransplantation.
3 The comments represent the approved viewpoint
4 of the AST and ASTS joint council and not of any
5 individual investigative group or corporate entity.
6 Next slide, please.
7 Organ transplantation is highly successful
8 technically, but donor organs are recognized as a
9 scarce national resource. Over 180,000 people have
10 died in the United States alone waiting for an organ,
11 and this scarcity disproportionately influences
12 historically marginalized populations and fuels
13 unethical donor practices in many countries.
14 Transplantations reach could be markedly expanded with
15 a more sustainable donor organ source. Next slide,
16 please.
17 The transplant community strongly supports
18 xenotransplantation as a means of improving access to
19 life-saving organs and agrees that recent advances in
20 the genetic engineering of potential donor source
21 animals and emerging pre-clinical and clinical data

1 support the initiation of focused, small-scale, human
2 trials in appropriately selected patients at a limited
3 number of qualified sites.
4 We recognize that there are both risks and
5 benefits but believe that the data support the benefits
6 to patients and society now outweigh the risks. Next
7 slide, please.
8 Organizations such as the AST and the ASTS
9 offer the public established expertise and will be
10 critical in moving this field forward appropriately.
11 We strongly advocate for partnership with medical and
12 scientific societies such as ours. Next slide, please.
13 Several recent findings underscore that it is
14 now appropriate to move to the clinic. This includes
15 the demonstration of that hyperacute rejection has been
16 largely overcome with new transgenic donor animals.
17 Human genes can now be reliably engineered into pigs,
18 shown to be expressed, and in some cases shown to
19 mitigate the risk of rejection. Nevertheless,
20 xenotransplantation requires immunosuppression that is
21 likely similar to, but distinct from,

1 allotransplantation. The information needed regarding
2 immunosuppressive needs can, we believe, thus be gained
3 through cautious clinical trials. Next slide, please.
4 Given that the pace of discovery in
5 xenotransplantation is rapid and there is still much to
6 be learned, we believe that the FDA should take an
7 adaptive regulatory stance to the initial small-scale
8 clinical experience. Many unique regulatory concerns
9 need definition, but the data presently are
10 insufficient for definitive resolution, and we believe
11 they will remain insufficient without intervening
12 clinical evidence. Thus, small-scale trials should be
13 permitted to inform the rational accumulation of
14 knowledge for regulatory oversight. Next slide,
15 please.
16 It is premature to expect that donor animals
17 used for initial studies will be the ultimate product
18 for widespread clinical application. As such, the FDA
19 should be reasonably permissive in the use of
20 intermediate animals, including the use of cloned pigs,
21 to develop a robust proof of concept prior to

1 establishing permanent guidance for animals for
2 clinical use.
3 The use of plausible gene cassettes should be
4 allowed prior to reductionist proof of the
5 contributions of each gene. Off-label drug use will be
6 required for early phase, proof-of-concept trials.
7 Next slide, please.
8 Xenotransplantation is inherently species-
9 specific. While much has been learned from pig to non-
10 human primate models, these experimental models have
11 demonstrable limitations and cannot be assumed to be a
12 high-fidelity representation of all elements of the
13 pig-to-human model.
14 We believe that the state of the science
15 justifies small clinical trials to provide more direct
16 answers to some questions. However, the pig-to-non-
17 human primate and decedent models remain important
18 adjuncts for questions that cannot be ethically
19 conducted in patients. Next slide, please.
20 Although designated pathogen-free pig
21 facilities will be essential when the pig organs are

1 commercialized, in these initial limited studies, it
2 should be sufficient to demonstrate that the pigs are
3 free of relevant pathogenic microorganisms with current
4 screening technology. It should be recognized that,
5 like in human allotransplantation, there is no
6 guarantee that donor pigs will be completely pathogen-
7 free. Next slide, please.
8 We have provided two slides summarizing
9 recommendations for minimizing infectious disease risk
10 in early phase clinical trials. In the interest of
11 time, these are submitted for offline consideration.
12 Next slide, please.
13 Again, this slide is submitted for the
14 Committee's consideration regarding infectious risk.
15 Next slide, please.
16 We have also summarized the major ethical
17 considerations for human brain-dead decedent
18 xenotransplant research for the Committee's
19 consideration. Next slide, please.
20 We have also compiled major ethical
21 considerations for xenotransplantation human subject

1 research, including social or scientific value toward
2 improving access to transplantation, scientific
3 validity, fair subject selection avoiding exploitation
4 of vulnerable groups, favorable risk-benefit ratios,
5 independent review and oversight, informed consent,
6 respectful research subjects, including humane donor
7 animal care and respect for a patient's desire for
8 confidentiality. Next slide, please.
9 We suggest that xenotransplants are best
10 performed as part of prospective clinical trials rather
11 than emergency procedures for expanded access to
12 unapproved products. Clinical trials will offer a more
13 deliberate prospective approach and better oversight as
14 well as better data collection and tissue archiving
15 that will be critical for phased implementation of this
16 technology. Next slide, please.
17 We believe it is important to keep costs and
18 accessibility in mind. While we recognize that the
19 companies entering this field should be able to map a
20 sustainable path forward, it should not be one that
21 fails to provide access to care for people in need.

1 Next slide, please.

2 The introduction of xenotransplantation should
3 be coordinated with the existing organ sharing network.
4 A xenograft should not, for example, influence a
5 patient's position on the allotransplant waiting list.
6 Ultimately, xenotransplantation will need to be woven
7 into the existing allotransplant fabric and thus
8 coordination with the OPTN will be appropriate. Final
9 slide, please.

10 Thank you for the opportunity to express these
11 views of the American Society of Transplantation and
12 the American Society of Transplant Surgeons. Thank
13 you.

14 **MS. CHRISTINA VERT:** Thank you. We will now
15 move on to the next speaker, Dr. Jayme Locke.

16 **DR. JAYME LOCKE:** Thank you. Good afternoon.
17 Thank you for the opportunity to present today. We
18 receive grant funding from United Therapeutics.

19 Next, Slide 2 outlines our goals.
20 Specifically, we will highlight diminishing returns of
21 testing ten gene-edited pig kidneys in a non-human

1 primate xenotransplantation model. The need for
2 xenotransplantation to adhere to firmly established
3 industry standards in human-to-human
4 allotransplantation and that pathogen-free facilities
5 should house source animals for human
6 xenotransplantation. Slide 3, please.
7 The pig-to-non-human primate model of
8 xenotransplantation has helped advance the field
9 substantially over the last 30 years but does have
10 significant limitations.
11 Next, Slide 4 highlights how gene editing has
12 allowed for successful pig-to-non-human
13 xenotransplantation, including providing life-
14 sustaining renal function. These data represent ten
15 gene-edited, pig-to-non-human-primate
16 xenotransplantation after NHP native nephrectomies and
17 clearly demonstrate creatinine clearance and
18 electrolyte homeostasis. However, genetic engineering
19 improved compatibility for humans, not for non-human
20 primates.
21 Next, Slide 5 demonstrates improvement in

1 crossmatching between humans and the genetically edited
2 pigs with increasing xenoantigen knockouts. The red
3 arrow points to a box that represents a negative
4 crossmatch or tissue compatibility. For humans, the
5 likelihood of the negative crossmatch or a tissue match
6 increases moving from wild-type pig to single knockout
7 to double knockout to triple knockout such that
8 approximately one-third of humans have a negative
9 crossmatch with a triple knockout genetically edited
10 pig.
11 In contrast, non-human primates never achieve
12 a negative crossmatch or a tissue match with the pig
13 kidney independent of the genetic modification. The
14 bottom figure demonstrates similar findings with only
15 humans having a negative crossmatch to the triple
16 knockout genetically edited pig. The red arrow points
17 to the line below which is a negative crossmatch.
18 Next, Slide 6 summarizes this important
19 limitation highlighting that pig to non-human primate
20 kidney xenotransplantation is a model of incompatible
21 kidney transplantation with the frequency of positive

1 crossmatches or tissue incompatibilities, being 100
2 percent among 183 non-human primates tested against
3 genetically edited porcine kidney xenograft over a
4 five-year period.
5 Not surprisingly and as highlighted by the
6 figure on the right of the slide, transplantation
7 across a positive crossmatch with no pretransplant
8 intervention is associated with hyperacute rejection or
9 immediate graft loss in some. And among those with
10 lower intensity, positive crossmatches who survive the
11 initial operation, poor long-term graft survival
12 results.
13 In some, continued use of the non-human
14 primate model to test graft survival of genetically
15 edited porcine kidneys is futile and not capable of
16 answering the much sought-after answer to the question
17 of whether porcine xenografts will be bridge or
18 destination therapy for living humans.
19 Given genetic modifications were designed to
20 optimize the porcine donor for the purpose of
21 transplanting humans, a preclinical human model was

1 needed. Next, Slide 7, please.

2 Importantly, as the next Slide 8 highlights,

3 the organ procurement and transplant network or OPTN,

4 mandates a pretransplant crossmatch as a standard of

5 care for kidney transplantation.

6 Next, Slide 9 emphasizes the rationale for

7 this, which is to avoid hyperacute rejection or

8 immediate graft loss. The picture demonstrates a black

9 kidney that has been hyperacutely rejected as the

10 result of transplanting across a positive crossmatch.

11 In order to avoid this, a prospective or pretransplant

12 crossmatch is necessary but had never been developed or

13 validated for use in pig-to-human xenotransplantation.

14 Next, Slide 10 details the establishment of

15 human brain death as a feasible preclinical human

16 model, also known as the Parsons' model, which has

17 allowed for the development and validation of a flow

18 crossmatch specific for pig-to-human

19 xenotransplantation, establishing the exact same

20 standard of care for xenotransplantation that currently

21 exists in human-to-human allotransplantation.

1 The figure on next Slide 11 demonstrates
2 identification of positive and negative controls for
3 crossmatching as well as a negative prospective flow
4 crossmatch predicting that hyperacute rejection would
5 not occur between the human decedent or preclinical
6 human model and the ten gene-edited porcine kidney.
7 Next, Slide 12 demonstrates validation of this
8 flow crossmatch. The upper-right panel shows the ten
9 gene-edited porcine xenograft pre-reperfusion in the
10 preclinical human model. Note the pale color.
11 The lower-right panel demonstrates the ten
12 gene-edited porcine xenograft in the preclinical human
13 model shortly after reperfusion. Note the pink healthy
14 color that is in stark contrast to the black
15 hyperacutely rejected kidney shown in the previous
16 slide indicating hyperacute rejection has been avoided.
17 This validated the prospective flow crossmatch
18 prediction that the ten gene-edited porcine xenograft
19 would not be hyperacutely rejected by the immune system
20 of the preclinical human model and established the
21 first-ever flow crossmatch for a ten gene-edited, pig-

1 to-human porcine xenotransplant. It is also important
2 to note that this xenotransplant was performed using
3 standard induction and maintenance immunosuppression
4 commonly and routinely used in human-to-human
5 allotransplantation.
6 Next, Slide 13. As highlighted on the next
7 Slide 14, the standard of care in human-to-human
8 allotransplantation also mandates organ procurement
9 organizations know and communicate the pathogen status
10 of potential deceased donors prior to allocation.
11 Specifically, as shown on the next Slide 15,
12 understanding pathogen status in human-to-human
13 allotransplantation involves the use of those PCR
14 methods to detect active viremia and serologic assays
15 for detection of prior viral exposure. The latter is
16 particularly important for latent viruses.
17 Next, Slide 16 describes our process for
18 replicating the standard of care in xenotransplantation
19 at UAB. Specifically, the ten gene-edited porcine
20 kidneys come from a herd maintained at a pathogen-free
21 facility. Porcine herd pathogen status is confirmed

1 with quarterly screening and just prior to procurement.
2 The procurement of kidneys from the ten gene-edited
3 porcine source animal occurs within the pathogen-free
4 facility ensuring no infectious breech.
5 Post ten gene-edited, pig-to-human
6 xenotransplantation, blood from the preclinical human
7 model was tested for the presence of porcine endogenous
8 retroviruses and was determined to be negative as shown
9 in the gel lanes labeled Day 0 through Day 3T, which
10 represent human blood samples from the day of
11 transplant and then post-transplant through study
12 termination.
13 Recent data published in *The New England*
14 *Journal of Medicine* and summarized in the next Slide
15 17, however, demonstrate that in the absence of
16 maintaining source animals in a pathogen-free facility
17 pig-to-human viral transmission is possible. Griffith
18 and colleagues reported in the NEJM earlier this month
19 transmission of porcine CMV DNA in the first pig-to-
20 human heart xenotransplant.
21 The authors say that the source animal

1 pathogen status was confirmed prior to procurement via
2 PCR methodology only. PCR only detects active viremia
3 and does not provide details regarding prior exposure.
4 Only serologic testing provides this information. The
5 authors did not report serologic testing as part of
6 source animal pathogen status confirmation.
7 In addition, the authors acknowledge that the
8 source animal did not come from the pathogen-free
9 facility but rather was transferred from a bio-secure
10 facility to the University of Maryland Research Animal
11 Facility where the porcine source animal heart was
12 ultimately procured.
13 Next, Slide 18 further emphasizes the need for
14 both PCR and serologic testing as well as pathogen-free
15 facilities for ensuring low infectious risk in source
16 animals are available through human transplantation.
17 Porcine CMV can be eliminated from the herd via
18 selection isolation in Caesarean delivery as previously
19 discussed.
20 However, prior exposure is critical as porcine
21 CMV is a latent virus. Viral latency is a type of

1 persistent viral infection, which after initial
2 infection, viral proliferation ceases but the genome is
3 not eradicated. In other words, the source animal
4 would test pCMV negative by PCR but may have a positive
5 serologic test if prior viral exposure occurred.
6   Serologic tests detect antibody formation from
7 prior exposure to the virus and are good markers for
8 the presence of latent virus. Importantly, latent
9 virus can then reactivate and produce viremia without
10 the host becoming reinfected by an outside virus. A
11 positive serologic test and negative PCR for a latent
12 virus indicate the potential danger of viral
13 reactivation post-transplant, particularly in an
14 immunocompromised human host.
15   While the use of actively viremic source
16 animals had been avoided via PCR testing, it may be
17 prudent to avoid the use of source animals with prior
18 exposure to latent viruses as confirmed by positive
19 serologic screening to avoid pig-to-human viral
20 transmission.
21   Next, Slide 19 summarizes our recommendations.

1 Number one, continued testing of ten gene-edited pig
2 kidney xenografts and non-human primate models is
3 futile. We recommend parallel studies in preclinical
4 human models and a Phase 1 adaptive clinical trial in
5 living humans.
6 Number two, standard of care practices that
7 have been firmly established in human-to-human
8 allotransplantation should be leveraged in developing
9 policies and procedures for xenotransplantation.
10 Specifically, we recommend requiring a prospective or
11 pretransplant flow crossmatch to ensure tissue
12 compatibility prior to performing xenotransplantation
13 in living humans.
14 Source animal pathogen status should be known
15 and communicated prior to performing
16 xenotransplantation in living humans. Optimal control
17 of pathogen status necessitates the requirement for
18 pathogen-free facilities to house source animals as
19 well as the addition of serologic testing for porcine
20 CMV. Thank you for your time.
21 **MS. CHRISTINA VERT:** Thank you. This

1 concludes the Open Public Hearing for today, and I will
2 now hand the meeting back over to Dr. Butterfield.
3 **DR. LISA BUTTERFIELD:** Terrific. Thank you
4 very much. I really appreciate the two presentations
5 we heard with some very useful information.
6 We'd now like to move to the beginning of the
7 discussion of our second question. And for that,
8 first, we'll have our invited speaker, Professor
9 Denner, on methods for the detection of infectious
10 diseases. Professor Denner.
11
12 **INVITED SPEAKER PRESENTATION: METHODS FOR THE DETECTION**
13 **OF INFECTIOUS DISEASES**
14
15 **DR. JOACHIM DENNER:** Thank you very much. And
16 I would like to note some methods which are necessary
17 to detect viruses which are difficult to detect.
18 I would like to speak about sensitive
19 detection systems for infectious agents in
20 xenotransplantation.
21 Before I start my talk, I would like to remind

1 you that although in allotransplantation, numerous
2 viruses have been transmitted to the transplanted
3 patient. Herpesviruses, HIV-1, even rabies virus,
4 hepatitis virus, and even Bryant. Though it seems that
5 eventually xenotransplantation may be much safer
6 compared with allotransplantation because we know which
7 pig is safe.
8 Here you see an overview of all papers were
9 published in the recent years. First, to show PCR-
10 based detection methods: PCR, RT-PCR, real-time PCR, or
11 droplet digital PCR. Immunological methods: Western
12 blot analysis, ELISA, immunoperoxidase assay, and
13 immunohistochemistry, and we also published numerous
14 reviews where we carefully analyzed the potential risk
15 posed by these viruses.
16 The lesson from the first pig heart
17 transplantation where a porcine virus, porcine
18 cytomegalovirus, was transmitted showed that in all
19 these clinical trials, competent virologists should be
20 involved. We need sensitive and specific detection
21 systems, and we have to know how, when, and where to

1 test in the donor pigs.

2 The first clinical trial, the transplantation

3 of islet cells from Auckland Island pigs in New Zealand

4 and in Argentina, there were 26 microorganisms included

5 from these pigs. They are the cleanest pigs in the

6 world, and we checked all the patients in New Zealand

7 and in Argentina. There was no transmission of porcine

8 viruses, including porcine endogenous retroviruses.

9 When I say detection systems, I mean a

10 complex, which includes not only the specific detection

11 methods or based on PCR methods or cell-based methods

12 or in immunological methods, but this includes all the

13 sample generation, the sample preparation, the sample

14 origin, the time of sampling, and most importantly

15 negative and positive controls.

16 I would like to demonstrate all these

17 detection systems using porcine endogenous retrovirus

18 as an example. It's simply to demonstrate their life

19 cycle. The virus infects the cells using a receptor,

20 and then the viral genomic RNA is described by a

21 special enzyme reverse transcription into DNA. And

1 this DNA can be integrated into genome of the cellular
2 DNA of the cell. And from there, viral proteins and
3 virus particles were produced and released by a
4 (inaudible).
5 As we already heard, we have PERV-A and PERV-B
6 present in all pigs, PERV-C present not in all pigs,
7 recombinant viruses which recombine into receptor
8 binding domain of the enveloped protein and, therefore,
9 acquire the ability to infect human cells. And the
10 pathogen on the human cells increases the LTR and
11 increases the titer of (inaudible).
12 And there are different possibilities to
13 detect virus. First, PCR using primers in the pol
14 region was highly conserved among all PERVs, and
15 therefore, we detect all integrated proviruses. Using
16 primers specific for the enveloped proteins allows us
17 to discriminate between both A, B, and Cs. Using real-
18 time PCR or droplet digital PCR, we can quantify the
19 provirus in the genome. And using our RT-PCR and real-
20 time RT-PCR, we can detect and quantify the viral RNA,
21 the expression on the RNA level.

1 And using Western blot or other immuno
2 methods, we can detect virus protein expression. Using
3 a reverse transcriptive assay, we can detect reverse
4 transcriptase activity. And electron microscopy shows
5 us virus particles.
6 And most important assay is in the infection
7 assay which can show that the virus is infectious.
8 Using human cells, we show that it can infect human
9 cells, and, using pig cells, it shows that it can
10 infect pig cells.
11 Important also is the validation of the
12 detection methods. Here, for example, a real-time PCR
13 to several operators tested all samples in the real-
14 time PCR for three times, or in the standard course,
15 three operators tested the material and showed that the
16 results are nearly identical. And this shows that this
17 method works.
18 The indirect detection method detects
19 antibodies against the virus, an indirect sign of
20 infection. For example, in the case of porcine
21 endogenous retroviruses, we used recombinant proteins,

1 the surface, the Gac, and the transmembrane envelope
2 protein which were produced as time as recombinant
3 proteins. And we checked our positive sera, goat
4 antisera against these recombinant protein, and here
5 human sera after pig islet cell transplantation in New
6 Zealand, and you see there was no antibody detection,
7 which means no PERV infection. Alternatively, we can
8 also use virus lysate and the goat antisera, and we get
9 the same results showing that our system is working and
10 that there is no transmission of the virus.
11 Using droplet digital PCR, we were able to
12 quantify the copy number of the PERV, for example, in
13 Aachen minipigs and in Göttingen minipigs around 60
14 verses in cell line PK15 around 40/50. This is
15 published but the copy number, it doesn't say a lot
16 because important is the ability of the provirus to
17 produce infectious viruses which are able to infect
18 human cells.
19 We also studied the expression of the PERVs in
20 endogenous retroviruses using real-time PCR. So you
21 measure the messenger RNA and the genomic RNA in the

1 cytoplasma, and you see the expression is very, very
2 low. Again, minipig has a high expression compared
3 with the cell line PK15 which is able to produce virus
4 particles.
5 Now it starts a little bit complicated, but I
6 simply would like to mention that gammaretroviruses,
7 like PERV, they are able to produce full-length
8 messenger RNA which produces the gag and the pol
9 protein and a spliced messenger RNA which then produces
10 the envelope proteins. And through measuring the
11 presence of spliced messenger RNA, you can already see
12 there is an envelope protein. When the envelop protein
13 is present, the likelihood that viruses will be
14 produced is larger in comparison to the absence of the
15 spliced messenger RNA. We also have methods to detect
16 PERV-A/C with different PCR strategies.
17 The expression of PERV proteins, here we have
18 Yucatan minipig. You remember it had a very high
19 expression of messenger RNA, and we see although that
20 in numerous tissue of the pig using antibodies against
21 PERV in immunohistochemistry indicates expression of

1 virus protein in a living pig.

2 And as I already mentioned, the detection of

3 human-tropic PERV, usually the 293 cells were used,

4 which lost all restriction factors, therefore, they are

5 very susceptible, and it is very difficult to infect

6 normal cells. It's not impossible but very, very

7 difficult and here you have, I think, of PERV from a

8 Göttingen minipig.

9 So although I developed methods to detect

10 PERV-C, these are different PCR and real-time PCR. And

11 we collected several primer pairs because the genome of

12 PERV-C is not unique as they are different subtypes,

13 which can be detected with our approach.

14 Similar, we did it for the hepatitis E virus,

15 although at three different methods with a different

16 primer pair to detect viral RNA, and we used

17 recombinant proteins to look for antibodies against the

18 hepatitis E virus in in a Western blot assay.

19 It is important to understand that there are

20 latent viruses, which, after a while, disappear in the

21 organism, but infection of a latent virus means that

1 the virus is present the whole lifetime. It doesn't
2 disappear; it only hides. Though, if you look at the
3 virus titer in the replicating virus, you have an
4 increase, the latent virus disappears, and, when you
5 then have a detection method with a detection limit
6 here, then, when you transplant, you don't find the
7 virus. This is what happened with the Baltimore
8 patient. The method used was unable to detect the
9 latent virus, which then was activated in the human
10 host.
11 We also studied the transmission of PCMV/PRV
12 as I already mentioned to baboons. You see that there
13 is a high copy number in the baboon with the
14 transmitted PCV-positive organ. You see a lot of virus
15 proteins expressing proteins in the pig heart of the
16 transplantation, and you see renal cells in all organs
17 of the baboon using antibodies specific against PCMV,
18 indicating that virus-producing protein cells are
19 present everywhere. And we suggest that these are
20 disseminated porcine cells in the baboon.
21 Therefore, it is very important in the case of

1 the latent virus to use an immune system we developed
2 and published in 2016, a Western blot assay using two
3 recombinant proteins of the nano protein chiefly
4 (phonetic). And using these antigens, we screen
5 Göttingen minipigs using many positive results, Aachen
6 minipigs many positive results, and slaughterhouse pigs
7 nearly all animals are infected using these two
8 proteins here, the purified recombinant proteins here,
9 an example of a Western plot as shown here.
10 There's another problem that in young pigs,
11 you have colostrum transmission from the mother to the
12 piglet, and, if the mother is infected, she also will
13 transmit colostrum-containing antibodies against PCMV
14 here for piglets at Day 20. You can think that they
15 are infected, but, obviously, these colostrum
16 antibodies disappear after 20 days later. Only in one
17 case has antibody amount increased indicating that this
18 pig is really infected and virus is replicating and
19 antibody response is increasing. These are not
20 infected.
21 So to summarize using a PCR, you can in pigs

1 detect the PCMV only in the very beginning later in
2 life. It is in latency that you are unable to detect
3 the virus. If you have an uninfected, you, of course,
4 never see PCR positive. In Western blot (audio skip).
5 **MR. MICHAEL KAWCZYNSKI:** I think we lost -- we
6 lost you, sir. Hold on a second. He dropped his audio
7 there momentarily. So I'll turn my camera on here.
8 Christina, you got it?
9 **MS. CHRISTINA VERT:** We'll give him just a
10 minute.
11 **MR. MICHAEL KAWCZYNSKI:** I resent him a --
12 **MS. CHRISTINA VERT:** I just wanted to stop him
13 then.
14 **MR. MICHAEL KAWCZYNSKI:** Yeah. No, that's
15 quite all right. See if you can reconnect your audio,
16 sir. I'll send you the audio wizard again, sir. So
17 you can just reconnect your audio. We don't want to
18 miss any of that. I think he's connecting. Let's see.
19 Yep, he's dialing in now. All right. Just waiting to
20 see if his reconnects. I can give him a microphone.
21 Christina, you're still there and hear me, correct?

1 **MS. CHRISTINA VERT:** Yes, I hear you.

2 **MR. MICHAEL KAWCZYNSKI:** Okay. All right. I
3 just want to make sure you're here still. Sir, can you
4 at least acknowledge you can hear me? Raise your hand
5 or something that you can hear me. Okay. So let's get
6 your au- -- I'm just going to give you microphone, sir.
7 I'll do it that way. Here we go. I'm just going to
8 connect your microphone. Let's try that. And then
9 that microphone. Just give me a second here. Now,
10 come -- here we go. I'm going to try to connect you
11 this way. Here, sir, can you say something?

12 **DR. JOACHIM DENNER:** Hello. Can you hear me?

13 **MR. MICHAEL KAWCZYNSKI:** There we go. Yep, we
14 got you that way. All right. Can you continue your
15 last slide, please? We just connected you a different
16 way.

17 **DR. JOACHIM DENNER:** This one or this one?
18 This one too?

19 **MR. MICHAEL KAWCZYNSKI:** Christina, I'll let
20 you weigh in.

21 **MS. CHRISTINA VERT:** To the current and

1 previous slide, there was a request, yeah.

2 **DR. JOACHIM DENNER:** Okay.

3 **MS. CHRISTINA VERT:** Thank you.

4 **DR. JOACHIM DENNER:** So this is a general

5 overview how and when you can detect PCMV. Using PCR,

6 you can find positive reactions in young piglets and

7 then they are infected. If you don't see PCR-positive

8 reaction to animal, it's not infected. But when you

9 test adult animals and you get a negative PCR result,

10 it does mean that the animal is not infected. This is

11 what happened in Baltimore.

12 When you use a Western blot analysis, do you

13 see in infected animals, the whole time positive

14 reaction? This exception may be between colostrum

15 positive and the real positive. If the mother

16 infected, then the piglet not infected, you see in the

17 beginning some antibodies in the colostrum, but then

18 it's gone. And if the animals are both uninfected,

19 then you never see positive Western blot analyses.

20 So we also tried to use non-invasive detection

21 method. For example, oral swabs and anal swabs, and

1 this was quite successful when we used an uniplex real-
2 time PCR in the young animals. In adult animals, this
3 will not work because the virus is in latency.
4 And here you see on the screen how to detect
5 simultaneously different viruses using blood from a
6 pig. So you can find hepatitis E virus, then, in the
7 RNA and DNA, you can find PCMV circovirus, lymphotropic
8 viruses. Then you can isolate PCMVs into the thing
9 with the DNA with the RNA. You can stimulate them by
10 mitogen which was shown to increase the expression of
11 PCMV as well as of PERV. And so you can go through and
12 detect all what you would like to detect. This makes
13 it quite easy to screen an animal in total.
14 So the question which was asked here although
15 do we include in our testing in addition to the
16 hepatitis E virus, and the porcine cytomegalovirus,
17 porcine roseolovirus, which are known zoonotic virus,
18 other viruses. For example, pseudorabies virus which
19 was shown to infect humans in China and inducing
20 nootropic diseases. It was eliminated in Germany and
21 other countries, but it is still present in wild boars,

1 so you have to isolate your animals which were
2 negative.
3 The lymphotropic viruses, circovirus,
4 parvovirus, they are also on our testing list. We also
5 tested for the SARS-coronavirus-2. But meanwhile, we
6 know that this virus does not infect pigs and we tested
7 them, however.
8 And to make our testing very easy, we are
9 using gene blocks as positive control so we have the
10 region of the virus in between the primers as
11 (inaudible) DNA so we can test for all these viruses
12 very easily.
13 The conclusion is to have sensitive detection
14 systems for numerous xenotransplantation-relevant
15 viruses (PCMV, PERV, hepatitis E, and others). We know
16 that PCMV, PERV, and hepatitis E are zoonotic (causing
17 disease). PERV, it is still unclear whether it poses a
18 risk for xenotransplantation, and as I said in my first
19 talk, we have no additional experimental strategies to
20 screen for the risk posed by these animals by these
21 viruses. And so we really have to wait for the first

1 clinical trials, and, of course, all detection systems
2 should be improved and extended.
3 I thank again my coworkers and collaboration
4 partners, and I thank you for your attention.
5 **DR. LISA BUTTERFIELD:** Thank you so much,
6 Professor Denner. Very thorough and very actionable.
7 Thank you so much for that.
8
9 **Q&A SESSION**
10
11 **DR. LISA BUTTERFIELD:** So we now have some
12 time for questions and comments from the Committee
13 specific to this presentation, about testing, and then
14 so I'm watching for hands. And then after that, we
15 will move to Question 2, have our discussants, and our
16 full Committee discussion of the question. So do we
17 have questions and comments for Professor Denner? It
18 was very clear and very specific.
19 **DR. JOACHIM DENNER:** I hope I didn't kill the
20 people.
21 **DR. LISA BUTTERFIELD:** There were also a lot

1 of assay opportunities for us to discuss. Okay. So I
2 guess perhaps we should then just move to the Committee
3 discussion. And I'm sure there will be additional
4 questions as we go through those questions.
5 All right. Thank you again, Professor Denner.
6 Why don't we move to the Committee discussion of
7 Question number 2 and dig in on that.
8
9 **COMMITTEE DISCUSSION QUESTION #2**
10
11 **DR. LISA BUTTERFIELD:** All right. So for
12 Question 2, archiving of source animal, product, and
13 patient samples for up to 50 years -- five, zero, 50
14 years -- is the current FDA expectation outlined in
15 FDA-issued guidance titled, "Source Animal, Product,
16 Preclinical, and Clinical Issues Concerning the Use of
17 Xenotransplantation Products in Humans." So this is
18 from December of 2016.
19 Archived samples can aid in the investigation
20 of adverse events, and the archiving recommendations
21 apply to xenotransplantation products, including those

1 that have had ex vivo contact with animal cells but are
2 not themselves of animal origin.
3 Please discuss whether the expectations for
4 archiving of patient samples should be modified in
5 terms of length of storage and/or sample sizes. And
6 we've got now four specific sub questions to this.
7 So here is our charge for this section.
8 Please discuss technologies that can be used to analyze
9 cell banks and final products that might be
10 sufficiently sensitive to allow for modification of
11 archiving the requirements.
12 Please discuss conditions that would alter the
13 expectations for patient follow-up.
14 Please discuss conditions, if any, under which
15 patient follow-up for disease transmission should not
16 be required.
17 And lastly, please discuss conditions under
18 which recipients of xenotransplantation products should
19 be allowed to donate blood or tissues and organs.
20 So some very specific topics for us to
21 discuss, and, to get us started, we have two

1 discussants. First, I will call on Dr. Bloom.

2 **DR. MARSHALL BLOOM:** Thank you very much, Dr.

3 Butterfield and Dr. Denner, for that excellent and

4 amazingly comprehensive presentation.

5 The charge that you gave that what the

6 Committee was issued was to look at a number of

7 different things, and they were laid out at the

8 beginning. We're talking about cells that have --

9 human cells which have exposure to non-human cells,

10 like the Strata gel and the Epicel, cells which have

11 come in contact with the other non-human cells and then

12 moving on up finally to the actual xenotransplants.

13 And it certainly seems like the bulk of the interest is

14 in the latter, the actual xenotransplants.

15 And so the one thing that occurs as I

16 mentioned earlier, each of those different types of

17 transplants really I think has to be discussed

18 separately because the considerations are different for

19 each one of those. However, recognizing that in trying

20 to look at the specific questions that you raised in

21 terms of the possible technologies that could be used

1 to analyze cell banks, I think really that Dr. Denner
2 really laid those out very well in one of his slides.
3 But what I think has to be recognized is that
4 we have to be able to -- it's FDA needs to consider
5 that you want to look at different times for DNA/RNA
6 proteins and then also be able to look for serology.
7 And in terms of infectious agents, as Dr. Denner,
8 pointed out, we have to think about agents which are
9 actively infecting endogenous viruses, like the PERVs,
10 and then latent viruses, like the porcine
11 cytomegalovirus are.
12 So certainly, there are a host of technologies
13 to be used, and they've been laid out very well. I
14 don't think I could add more to what Dr. Denner said.
15 So there's a series of technologies. In each of those,
16 I think needs to be looked at by FDA in terms of the
17 specific type of biological that we're addressing.
18 But there are a couple of common themes, I
19 think, which are going to be critical to no matter what
20 type of cell bank or final product we're looking at.
21 He again, laid those out extremely well in what I think

1 is his number 7 slide. We have to look at how the
2 sample was produced, sample generation, how the sample
3 was prepared. And I would note that in that respect,
4 FDA needs to recognize there are multiple reagent
5 systems available for storing samples to look at
6 protein's nucleic acids and so forth.
7 I think any kind of sample preparation really
8 has to recognize the need for a number of different
9 replicates for verification of results as well as
10 sequential testing. Sample origin needs to be looked
11 at. The time of sampling controls and then along with
12 the specific detection methods, which as I mentioned,
13 he laid out very well. So to me, it's a little bit
14 hard to give sort of a blanket recommendation or even
15 an idea of how to address these in any sort of unified
16 way.
17 The current FDA recommendation is for 50 years
18 -- storing the samples for 50 years, and that's based
19 on a document which was promulgated back in 2016.
20 Certainly, the detection methods which are available
21 now are much better. So I think it's reasonable to

1 consider that that 50-year requirement could be
2 modified and to probably be shortened. But I don't
3 feel comfortable making any kind of specific
4 recommendation in that regard.
5 So now trying to hopefully having evaded Part
6 A, the other parts of B, C, and D are really clinical
7 issues that I really have a lot of -- I don't feel
8 really, really comfortable making too many comments on
9 those. I mean, I think in terms of C, "Please discuss
10 conditions, if any, under which patient follow-up for
11 disease transmission should not be required," if we're
12 talking about xenotransplantation, I'm having
13 difficulty seeing any kind of condition in which the
14 follow-up would not be required.
15 And then, "Please discuss conditions that
16 would alter the expectations for patient follow-up,"
17 which was number B, certainly, if any type of illness
18 was identified in the patient, that would mandate
19 increased follow-up. And if any type of one of the
20 infectious agents, which have been mentioned, was
21 identified in the source material, that also would

1 necessitate increased follow-up of the patient and
2 then, as we discussed earlier, possible examination for
3 therapeutic modalities.
4 And I think that's really about all I can
5 contribute to this discussion.
6 **DR. LISA BUTTERFIELD:** Well, thank you very
7 much, Dr. Bloom. I appreciate those initial thoughts
8 to get us started. And so now, we'll move to our
9 second discussant, Dr. Maragh, and then after that,
10 we'll get the ball rolling with the rest of the
11 Committee.
12 **DR. SAMANTHA MARAGH:** Great. I have to second
13 Dr. Bloom's comments. Professor Denner did an
14 excellent job of setting the stage in describing the
15 challenges and the techniques that are options and need
16 to be used.
17 I wanted to set the context. I'm coming at
18 this; I'm not a virologist. I'm not in the
19 xenotransplantation space specifically. I am coming at
20 this from somebody that does a lot of nucleic acid
21 measurements and has to deal with sample storage as my

1 thoughts on this kind of question.

2 Dr. Denner gave a great review of the kinds of

3 technologies, and I think one of the things that really

4 struck me in this space for the specific need is

5 something I was thinking about as I was looking at the

6 recommendations which is, as I was looking at the

7 guidance, I saw in some places where it looks like one

8 times ten to the seventh cells and at least five

9 aliquots at different stages.

10 One of the things I wanted to bring up for

11 discussion is that, depending on the technology and

12 there will be varied technologies that are needed, you

13 want to think about maybe how much sample you need

14 because not all of those will need the samples handled

15 in the same way when you go to use the extraction

16 handling or use. You may have ten million cells that

17 you want to do five different things on, but they can't

18 actually all be done on the same aliquot of cells

19 because they need to be handled and processed in a

20 different way to get to the biomolecule or analyte that

21 you need to measure.

1 So that's just one thing to consider that the
2 kinds of measurements you need to do, how the sample
3 needs to be processed to get at those targets may drive
4 kind of whether you want one vial with ten million or,
5 you know, five vials of two million, something like
6 that, because you may not be able to get everything you
7 want out of that one vial because you've got to do
8 different processing.
9 The other thing I was thinking about is in
10 terms of this question about storage time and what you
11 want to do, a lot of what's been driving the
12 conversation I've been hearing today is the known.
13 These are the viruses that you know that you want to be
14 able to detect. Judy in her opening presentation did a
15 great job of basically bringing up the idea of the
16 unknown unknown. You want to be able to have sample
17 because you may not know something you want to detect
18 later, and you may find out because you have the sample
19 bank and you go back, that it was actually present, but
20 it didn't have any impact.
21 I think that just as valuable as knowing

1 something's present that you might want to avoid, to be
2 able to retrospectively go back to the sample and say,
3 oh, this was present all along, and it actually didn't
4 impact patients as the follow-up was going on and so
5 that you can know that that wasn't an indication that
6 was concerning. So I think both sides of that are very
7 valuable uses of having samples banked.
8 In terms of technologies, so we heard about
9 RT-PCR, digital PCR, reverse transcription PCR, as well
10 as the need for protein types of assays and serological
11 kinds of assays. And my expertise isn't on the protein
12 and serological kind of assay types, but I will give a
13 little bit more on the nucleic acid detection systems.
14 Digital PCR/RT-PCR are still the state of the
15 art for the detection of highest confidence in terms of
16 copy number detection of unknowns, so you have to know
17 what sequence you're looking for. Or if you have a
18 contaminating sequence that might be competing, you
19 could know that you've got less signal than you expect
20 because there's something else competing with it,
21 depending on what your assay is.

1 Again, Dr. Denner outlined some really
2 creative designs for getting at detecting the kind of
3 target that are relevant for this question. I do want
4 to put out there that I think a question that will have
5 to be answered is, what limit of detection do you need?
6 What's good enough, and how do you know that your assay
7 is giving that?
8 I'm a measurements assay kind of person, and I
9 think about it as binary plus/minus, and at what level
10 of detection do you really need that assay to perform,
11 and does this community have the controls for those
12 assays to understand how well they're performing for
13 you to feel comfortable moving forward? I don't know
14 if you do, but that certainly, to me, is a
15 consideration. In some instances, binary, if that's
16 the application, I don't get that's quite the sense.
17 You might want to know how much of this is present, and
18 do you actually have the tools in terms of controls
19 that you would know the limits of detection of the
20 assay?
21 Another thing that I will bring up is there

1 are some newer higher sensitivity NGS sequencing kinds
2 of applications. One is duplex sequencing that we've
3 been working with and evaluating at NIST, and in some
4 instances -- we've done tests with digital PCR. We
5 push the system where, given the parameters that you
6 know you wanted to detect something, we can get down to
7 one in a thousand and less. And those levels actually
8 were targeted NGS.
9 With duplex sequencing, it's a newer way of
10 processing and barcoding samples. The information in
11 the data we've seen so far can get down to one in
12 10,000 and one in 100,000 but there's a big trade-off
13 in terms of cost. So the more you need to detect, the
14 higher sensitivity, there's going to be a trade-off in
15 costs because you've got to process more samples. And
16 there's going to be a trade-off in how much sampling
17 you need to push into that process.
18 I'd also want to stress what I've heard is the
19 importance of taking the right sample at the right
20 times to answer the question you're trying to ask. And
21 I don't know what that answer is for the (inaudible),

1 but that's the way I think of framing this is, how much
2 sample do you need, stored in which way, at what time
3 in order to be able to answer that question?
4 Then Dr. Denner's slide where he was showing
5 the piglet and the mother really sort of set the stage
6 for why that's so important. I think that in my mind
7 in terms of how or why things might change and the
8 current guidance if that thought process is driving
9 that, then that could be a way of framing if there is
10 anything to change.
11 My expertise is not in inpatient follow-up,
12 but I would just say that from what I heard today,
13 there isn't enough data in order to not follow up at
14 this point. Should there be enough data that makes you
15 confident to say we never see this, or we always see
16 this? Then I would just let the data drive those
17 things.
18 But from the conversations I've heard today,
19 it doesn't seem like there's enough data in the
20 community to say, we'd be really comfortable not having
21 follow-up or being comfortable where somebody today

1 could continue to donate because I think that has to be
2 a data and information-driven process.
3 So those are my comments, and I just want to -
4 - one other thing is on terms of contamination. If
5 people are aware or not aware, there's an anti-standard
6 on cross-species contamination. That's available.
7 There's about to be an update to that anti-standard
8 coming out very soon where in a multiplex PCR, you can
9 detect human and pig and cow and a series of other
10 species in terms of a contamination assay that's not
11 very familiar to everybody. Lisa, I'll leave my
12 comments there.
13 **DR. LISA BUTTERFIELD:** Terrific. Thank you so
14 much, Dr. Maragh. I appreciate those comments.
15 So now, let's hear from Dr. Ahsan and then
16 again, Dr. Bloom.
17 **DR. TABASSUM AHSAN:** Thanks. I had a quick
18 question. So we're meant to discuss here archiving the
19 duration, the utility of it. Perhaps, I need a little
20 bit more information on the purpose of archiving.
21 I'm hearing two things that would lead me to

1 separate answers. One is to understand adverse events.
2 Clearly, we want to monitor the patient. We want to
3 actually test the material that's transplanted or the
4 cells we're exposed to in order to understand adverse
5 events. But I don't imagine that we would be testing
6 samples that are 20 years old to assess adverse events
7 in a patient, right?
8 Now, on the other hand, there is a lot of
9 value in having, as viruses emerge and we have deeper
10 understanding, to go back and test archive samples to
11 understand how they may have played a role in various
12 transplant scenarios, but that is more of an
13 exploratory question, which I think is completely
14 valid.
15 The question is, how much of an onus can we
16 put on the sponsor for the exploratory elements as
17 opposed to the adverse events. So maybe someone from
18 the FDA can help me better understand the precise
19 objective of the archiving and upon who that onus is
20 laid?
21 **DR. LISA BUTTERFIELD:** Thank you for raising

1 that. Yeah, would there be some sort of centralized
2 long-term banking for the exploratory purpose that
3 would no longer be the responsibility of the sponsor
4 perhaps?
5 **DR. TABASSUM AHSAN:** Exactly.
6 **DR. LISA BUTTERFIELD:** Or is this always
7 going to be the responsibility of the sponsor? So I'm
8 not sure if anyone from the Agency would like to weigh
9 in. I have hands next from Drs. Bloom and Fishman.
10 Their hands are going up and down. I'm going to look
11 to the chat to see if someone from the Agency wants to
12 weigh in or if we should -- okay. Thank you, Judy.
13 **DR. JUDITH ARCIDIACONO:** It's Judy
14 Arcidiacono. So the idea behind archiving -- so we
15 have the look back for infectious disease and then the
16 possibility of the sponsor needing to go back as part
17 of their research program. But there's a possibility
18 of latency, especially with the endogenous retroviruses
19 and things like that.
20 So those are really our goals in the very
21 beginning. And I have to say, I agree with, who's

1 going to use the sample that's 50 years old? I think
2 one of the things that we also need to consider is,
3 well, what is the right amount of time? How stable
4 would samples be over time?
5 And unfortunately, the onus of all these
6 requirements would be on the sponsor because the Agency
7 certainly doesn't have the ability to store things like
8 that. But there could be consortia models or things
9 like that where developers pull their resources and
10 maybe fund a bank (inaudible). So there are options
11 there, but definitely the onus is on the sponsor or the
12 developer.
13 **DR. TABASSUM AHSAN:** So I worry about at the
14 end of the day, this is all about helping our patients
15 with access to treatment. Do we feel that a 50-year
16 storage duration would disincentivize therapeutic
17 developers to move forward because it's cost-
18 prohibitive?
19 **DR. JUDITH ARCIDIACONO:** Well, I mean, that's
20 not the intention, but I -- if we go back to the
21 archiving thing both for the products that are defined

1 (audio skip) by contact with cultured animal cells.

2 So that had been taking place for a very, very

3 long time, and we so we had a lot of data to show that

4 it wasn't necessary. The absence of data, it's really

5 hard to prescribe at times. Like I said, 50 years does

6 seem excessive, and, as a scientist, I don't think we

7 care about a sample that's 50 years old.

8 But things that -- recommendations, what that

9 should be and what is reasonable, we would appreciate

10 that at the Agency. So the point of this meeting is

11 really to look at some of the things that may be

12 prohibitive, also, trying to make sure we have a good

13 understanding what the risks are. So the storage of

14 sampling is kind of a risk mitigation strategy where if

15 something happens, you (audio skip).

16 In the beginning, we thought that we would be

17 wanting people to store actual tissue samples in vials

18 themselves, but there is a possibility where we're

19 saving nucleic acids or something like that where it

20 may be a little bit less burdensome. Hopefully, in the

21 absence of data, that's what would drive our decisions.

1 So we can certainly talk about it. (Inaudible).

2 **DR. TABASSUM AHSAN:** Yeah. So one thought

3 that occurs to me is to not prescribe the duration but

4 to make this a pre-IND discussion point because

5 depending on the patient population, if the prognosis

6 of the patient is quite poor and the transplant is

7 we're talking about extending life a year to two years,

8 50 years seems excessive in terms of the adverse

9 events, of course. On the data collection, that's a

10 whole other issue I think thinking about we want to

11 make that accessible but to burden a sponsor with

12 storing clinical samples for that duration is a hefty

13 burden.

14 So we might want to think of this as -- I

15 mean, is it possible to think of this as a pre-IND

16 question as opposed to a prescribed duration in a

17 guidance so that we can open it up based on -- because

18 that's general guidance not specific to a certain

19 indication or a specific patient population nor even to

20 a specific product because it spans from cell mined all

21 the way to whole organs.

1 So is there a manner in which we can keep this
2 a little bit more open-ended to promote conversations
3 to allow flexibility to allow products to get to
4 patients yet still maintain the integrity of patient
5 safety as well as data collection? Is that an option?
6 **DR. JUDITH ARCIDIACONO:** Yes, absolutely.
7 That really is one of the questions. Fifty years but
8 if not 50 years, how long? I think that one of the
9 things -- I understand the burden of holding onto
10 samples but also you would discuss with the Agency a
11 preclinical or an interactive meeting maybe. What kind
12 of records? So not actual samples but record do you
13 need to keep?
14 One of the things that might be good for the
15 xenotransplant community to get together and figure out
16 for themselves, as a group, what could we propose to
17 FDA that we think would be reasonable and rational for
18 storage, and how much information which I mean about
19 records?
20 You might store records on patients you had
21 adverse events, and then you go back and look at that

1 data and say, what's the pattern here? I think what we
2 really need to talk (audio skip) things: the
3 information, the stuff we keep in a database, what you
4 keep in a biobank.
5 But the Agency is always willing to open --
6 and open to listening to ideas that make sense. You
7 hear a lot from FDA, it's case by case, it depends, but
8 that is truly the situation. We'll measure the risk
9 and weigh the mitigation strategy.
10 **DR. TABASSUM AHSAN:** And not to take up too
11 much time, Dr. Butterfield, but just really quick one
12 more point. To then also think about in the pre-IND
13 conversation exactly to your point which is they could
14 decide to invest in more testing up front as product
15 characterization not necessarily released and have that
16 documented data and maybe maintain less in archived
17 sample form. Or they choose to defer that testing and
18 maintain more in archive sample form.
19 So I think that there's a lot of ways to get
20 to the solution of what it is that we need without
21 being too prescriptive to make it one solution that

1 everyone needs to press-fit into depending on their
2 different applications. So I think having it be a pre-
3 IND conversation but thinking about data versus
4 archive, thinking about the duration in the context of
5 the prognosis and the indication.
6 It might be something like, you know, a five-
7 fold or a ten-fold duration of the extended life
8 expectancy or something like that maxed at a certain
9 number. I think that there are ways to create formulas
10 here quote/unquote of how to get to the solution
11 without necessarily being prescriptive of just one
12 timeline, if that makes sense to others.
13 **DR. JUDITH ARCIDIACONO:** Absolutely.
14 **DR. LISA BUTTERFIELD:** Thank you. Thank you,
15 Dr. Ahsan, for that creative thinking in flexibility.
16 I think what I'm hearing is no one likes 50 years for
17 everything as a prescription, but we have to think
18 about data versus specimens, type of specimens, and the
19 temperature at which those specimens, for example, are
20 stored.
21 So let's move on to Dr. Bloom and then Dr.

1 Fishman and then we'll carry on from there. Dr. Bloom.

2 **DR. MARSHALL BLOOM:** There are two things.

3 First of all, I wasn't looking at all my pages of

4 notes, but one of the things that obviously the Agency

5 is looking at is next-generation sequencing because you

6 had a rather lengthy bit on that in the discussion of

7 that method.

8 Certainly, that's a very, very sensitive

9 almost agnostic way to look for other infectious

10 agents, which you don't know are going to be there

11 because the PCR -- most of that requires specific

12 primers to be able to come up with an answer.

13 So I want to endorse what the second

14 discussant said is that some of those methods are very,

15 very sensitive, but they're difficult to do, difficult

16 to analyze and make it like next-generation sequencing,

17 and they cost a fair amount of money. The question

18 then becomes, does the FDA want to require sponsors to

19 look for needles in haystacks. That's one thing.

20 And then the second thing, I really like what

21 Taby said about some of the expectations. But the

1 final point I want to make is looking at the individual
2 cells which are like grown on a monolayer of something
3 else as opposed to the islet cells and like a cartridge
4 as opposed to the actual xenotransplant.
5 It seems to me that you all really should
6 consider those -- the archiving conditions and the
7 requirements for those -- separately because I think by
8 doing that, the answers to some of the specific
9 questions that you ask will fall out a little easier.
10 Thank you.
11 **DR. LISA BUTTERFIELD:** Thank you, Dr. Bloom.
12 Dr. Fishman and then Paul Conway.
13 **DR. JAY FISHMAN:** Thanks very much. It's a
14 very interesting discussion.
15 I'd like to go back and think as Dr. Ahsan
16 talked about why we have these various samples because
17 I think that determines what we're saving and how we
18 use them. For diagnostic purposes, we're going to be
19 keeping our own samples on the site of the
20 xenotransplant trial, and we're going to use those to
21 analyze against subsequent clinically symptomatic

1 infections.

2 Therefore, they're going to be duplicate

3 specimens, and we do that already to look at things

4 like antibody-mediated graft rejection. So that any

5 transplant center has archived specimens, and they use

6 them for those purposes. So whether it's 50 years or

7 whatever it is, the other stored specimens are purely

8 speculative.

9 I haven't used a stored specimen to diagnose

10 anything beyond the first couple of years after

11 transplantation. I've been doing this for over 40

12 years. So the 50-year requirement becomes

13 unnecessarily onerous and not particularly useful for

14 two reasons. One is those specimens will degrade even

15 frozen over a period of time, and the linkage with

16 medical records is a problem, as well as preservation

17 of HIPAA requirements preserving those medical records.

18 So, if CDC and FDA want those samples, they

19 have to contribute to the way in which they're going to

20 be stored and where they're stored and what happens to

21 those records. I don't think you can put all that

1 burden on the sponsor. It seems to me unnecessarily
2 onerous, and I'm not sure there's any justification for
3 it in the current clinical environment because we've
4 not shown any potential infections that are going to
5 spread from the recipient to the general public.
6 That's not to say it couldn't happen; it's just to say
7 we haven't shown that.
8 I think subsequent tracking of infection in
9 asymptomatic recipients can be very informative using
10 agnostic methods as you've just heard for non-directed
11 sequencing, but it has a flaw which is you need a
12 databank to compare those sequences against of porcine
13 pathogens. That doesn't exist.
14 So the FDA and CDC and others will have to
15 contribute to the creation of a databank for comparison
16 with NGS data. That doesn't currently exist, so the
17 number of -- while the pig genome has been sequenced,
18 all potential pig pathogens have not been sequenced.
19 I'm speaking as the person who sequenced PERV, so
20 there's a limited number of data elements that are
21 available for that.

1 So I think what we have to do is think
2 creatively, whether it's in the pre-IND or not, and my
3 first bid would have been that we direct this towards
4 samples in the initial trials. If we don't find
5 anything with non-directed sequencing that we plan in
6 advance the cutback, the duration of sample storage.
7 In other words, we start with sample storage
8 for the duration of the graft and the survival of the
9 patient because we're supposed to be focusing on the
10 patient and not on experiments. So I think it's very
11 important to keep our eye on the ball that the clinical
12 goal is relief of the organ shortage, and that's what
13 we should be addressing, not the experimental nature of
14 xenotransplantation to any degree.
15 We do need to track these potential
16 infections, but what are we going to find after ten
17 years? I don't know of any data that suggests we're
18 going to find anything. Thanks very much.
19 **DR. LISA BUTTERFIELD:** Great. Thank you.
20 Paul Conway, please. And then Dr. Palevsky afterwards.
21 **MR. PAUL CONWAY:** Thank you very much, Dr.

1 Butterfield. I'd like to go back to Judith if we
2 could. It's something that she had said in the morning
3 when we were first doing the presentation, and I want
4 to make certain I've got this right.
5 She had indicated that there was a decline in
6 xenotransplantation and innovation after the 2016
7 publication of the FDA guidance. And I just want to
8 make certain I have that right, and then I have a
9 couple of questions I want to ask very quickly after
10 that.
11 **DR. LISA BUTTERFIELD:** I thought that as well.
12 Judy, do you want to confirm for us?
13 **DR. JUDITH ARCIDIACONO:** Yes, so after FDA
14 published the 2003 guidance, we saw a decline in xeno
15 activity, but that was mostly because of the rejection
16 responses. So, at that time, we did not have the
17 ability to genetically culture animals in the way that
18 would prevent rejection so, it was only because the
19 science wasn't at the point it needed to be for us.
20 There were some pre-clinical studies, but they
21 certainly weren't human studies. And so that's

1 basically what happened. There was just really no
2 activity at all for a long time with the Agency. So
3 that's not to say there wasn't research and other
4 things going on. But as far as the Agency was
5 concerned, there was no activity.
6 **MR. PAUL CONWAY:** Okay. And then just a
7 couple of quick questions, so the 50-year requirement
8 was in that 2016 guidance, correct?
9 **DR. JUDITH ARCIDIACONO:** Yes, and it was
10 actually in the original guidance. When we updated the
11 2016 guidance, we mostly did it for making sure that
12 the scientific references that we had at the time were
13 current, and there was a lot of FDA guidance documents
14 that were published after the 2003 publication of the
15 xeno guidance. So that's a (audio skip) change.
16 **MR. PAUL CONWAY:** Okay. So is it fair to say
17 that the 50-year requirement was a carryover from a
18 period of time going back into the 2000s?
19 **DR. JUDITH ARCIDIACONO:** Exactly.
20 **MR. PAUL CONWAY:** Okay. So I just want to ask
21 a couple of other quick questions. In the 2000s when

1 that was developed, were patients at the table for the
2 discussion about all the types of requirements that
3 were coming together that could potentially impact
4 innovation in the xenotransplantation either in the
5 2000s or in 2016?
6 **DR. JUDITH ARCIDIACONO:** So 2016, we did not a
7 public discussion. In 2003, so that document evolved
8 over many years of public discussion. Patients were at
9 the table, but I have to say that when the xeno
10 discussion first came up, the only things that were
11 really being considered were islets and the human
12 profusion devices. The idea of transplanting an organ
13 wasn't ever even considered.
14 So at that time, we were just talking about
15 cells, cell lines, or islets, so we were nowhere where
16 when that was written where we are today scientifically
17 and the potential for organ transplant.
18 **MR. PAUL CONWAY:** Thank you very much for
19 answering that. So I'd like to tack onto a couple of
20 things that Dr. Fishman and Dr. Bloom said because I
21 think this is a great example of where not just science

1 has moved forward. The innovation in the space has
2 moved forward, but also the expectations of patients
3 and patient advocates have evolved as well.
4 And so you have these powerful forces here
5 that are not simply a matter of science and scientific
6 investigation, but there's an expectation for the
7 delivery of solutions to those who are waiting and
8 whose lives are on the line. It doesn't mean that all
9 risk is thrown to the side, but I think there has to be
10 a fundamental understanding of how patient expectations
11 and the science, but patient insights and patient data
12 has evolved.
13 That needs to be brought into this across the
14 spectrum including issues like 50 years because, I
15 think, if you issue guidelines that could stimy
16 innovation in the space and then you put all of the
17 onus on a sponsor, yet a lot of the interest that's
18 driving some of the requirements, for example, the 50
19 year, might be more speculative. Then the onus is on
20 the government I think to share some of that
21 responsibility and to enter into the arena in whether

1 it's to set up a consortium or whatever.

2 I think you have to constantly look at de-

3 risking the environment, accelerating innovation,

4 protecting patients, but moving things forward for the

5 ultimate customer here. The ultimate customer is not

6 the scientists; it is the patient.

7 In terms of risk tolerance, FDA has done great

8 work on this, but I think folks at CDC and other places

9 need to understand that patients have a very high-risk

10 tolerance. It doesn't mean that we expect safety to be

11 thrown off to the side, but the intensity of the desire

12 to address organ failure in those we know who are dying

13 is critical. We cannot miss that in the conversation

14 as guidelines are updated or as folks pursue different

15 research.

16 I think the client, the customer, the patient

17 has always got to be at the forethought. I'm not

18 certain that was the case in the early 2000s. It may

19 have been something where there was a failure of

20 imagination to see the day when organs would come.

21 But I know that since the 1990s, patients have

1 been listening to conversations about
2 xenotransplantation. I just want to put that out there
3 because you have a huge audience internationally and
4 nationally that's looking for progress in this area,
5 and again, the risk has to be monitored
6 Going to some of these questions here very
7 quickly, conditions in which you would expect
8 expectations to change for follow-up, well, of course,
9 you see emerging data and somebody has an organ that's
10 a year out or two years or 36 months out, you would
11 need the ability to quickly contact those people and
12 communicate with them that there's a risk.
13 As far as right now of dropping or lowering
14 the standards with having the follow-up, I can't
15 envision that based on the conversation here today, but
16 I appreciate you coming back on to answer that because
17 it really caught my ear anything that has stymied
18 innovation and how we can work better together so we
19 can create policy and advice that helps the Agency move
20 forward. Thank you.
21 **DR. LISA BUTTERFIELD:** Great. Thank you both.

1 **DR. JUDITH ARCIDIACONO:** It's Dr. Arcidiacono.

2 **DR. LISA BUTTERFIELD:** Yes.

3 **DR. JUDITH ARCIDIACONO:** So also want to point
4 out that the risk of xeno zoonoses is a public health
5 issue. So we certainly would not put forward
6 expectations that could never be met. But this is a
7 whole package issue. It's not just about the
8 collecting and archiving some samples but how will the
9 public be affected.

10 I don't want to take anything away from Day
11 number 2 discussions, but this is just a small part of
12 our concern. We appreciate hearing your thoughts, and
13 we are looking out for the patients. So thank you for
14 that.

15 **DR. LISA BUTTERFIELD:** Okay. Thank you. So
16 now we'll move to Dr. Palevsky then Dr. Denner and then
17 our consumer representative Ms. O'Sullivan-Fortin.

18 **DR. PAUL PALEVSKY:** So I appreciate Mr.
19 Conway's comments, and I agree with most of them. I
20 wanted to make sure. There was an implication in some
21 of the earlier comments regarding prognosis. Just to

1 remember that, for individuals who receive kidney
2 transplants, life expectancy is significant. Mr.
3 Conway is a perfect example. We need to make sure I
4 think that while our sample storage doesn't inhibit
5 innovation, that our sample storage is at least as long
6 as we expect patients to have continued functioning of
7 xenotransplants, which may be decades. So there does
8 need to be a balancing there.
9 **DR. LISA BUTTERFIELD:** And so that would align
10 perhaps with what Dr. Ahsan suggested about a case-by-
11 case and patient population-specific requirements?
12 **DR. PAUL PALEVSKY:** Yes, but recognizing that
13 it may be a long life expectancy post
14 xenotransplantation.
15 **DR. LISA BUTTERFIELD:** Hope so. Thank you.
16 Dr. Denner.
17 **DR. JOACHIM DENNER:** Concerning the new-
18 generation sequencing, I would simply repeat what I
19 said in my talk. In all of these situations, I saw
20 where this method was used to determine the pig virome.
21 Never, ever xenotransplantation-relevant

1 viruses like hepatitis E virus or the porcine
2 cytomegalovirus or the roseolovirus have been described
3 to the disease viruses, which obviously as I showed by
4 our Western blot are present in nearly all pigs, cannot
5 be detected by this method, only adenoviruses, the
6 coronaviruses, which are in high quantity. So I think
7 to detect specific cytogenes, we need specific PCR
8 methods.
9 **DR. LISA BUTTERFIELD:** Thank you for that
10 clarification. Okay. Ms. O'Sullivan-Fortin and then
11 Dr. Kimmel and Dr. Maragh.
12 **MS. KATHLEEN O'SULLIVAN-FORTIN:** Sure, thank
13 you so much. This discussion is so interesting. I
14 just wanted to echo what Mr. Conway had said about
15 making sure that the burden does not fall, in terms of
16 storage and follow-up, not only to the sponsor but also
17 patients are not outside the realm of those that are
18 responsible for helping that. Because, if there's no
19 system set up, then the patients will endeavor to set
20 up their own registry et cetera to attempt to supplant
21 the information that's being stored.

1 My concern is with again this 50 year that no
2 one seems to be a fan of. My concern is that people
3 would just take a different target to work on and that
4 xenotransplants, in some respects, won't be as
5 thoroughly developed as it could be because of this.
6 I'm not even 50, so I can't imagine someone
7 wanting to use the cell sample that outlives me.
8 Although I know that technology will advance, and
9 that's fine since we'll be able to do amazing things.
10 But I just worry that we're setting up standards so
11 high that we're protecting patients straight out of a
12 cure or a solution.
13 **DR. LISA BUTTERFIELD:** Thank you. Appreciate
14 that perspective. Dr. Kimmel and then Dr. Maragh.
15 **DR. PAUL KIMMEL:** I just wanted to make two
16 observations, and it's not from really a perspective of
17 great expertise. But I was thinking about the public
18 health issues and this 50-year discussion, and I'm
19 thinking that there was a group of people who are as
20 wise as us 17 years ago who decided that 50 years was
21 what they wanted.

1 I don't know exactly why they came up with
2 that timeframe, but I'm thinking of two issues. The
3 discovery in the arts that the first patients who were
4 infected were HIV were from the 1950s, and that was
5 sort of a 50-year perspective. They wouldn't have been
6 able to make those historical observations if they
7 didn't have bank samples.
8 I think also from a public health perspective
9 that secular trends will not be able to be evaluated if
10 there's not a long-term repository of data. So I think
11 I would be interested in more for the arguments for the
12 longer observation periods. I understand that they may
13 affect sponsors and perhaps they may affect innovation.
14 The other point that I wanted to make was I
15 heard the discussion of serologies by Dr. Denner which
16 was very nice and the plea by Dr. Locke for different
17 kinds of evaluations of donor animal tissue by looking
18 at serologies. And it occurred to me that negative
19 serologies do not indicate that there is not a latent
20 infection because antibody levels may decrease over
21 time, or, in immunosuppressed hosts or recipients, they

1 may not be elaborated. So I think I was getting the
2 impression that serological data are sort of gold
3 standards, and I don't think they are. So those were
4 my two comments.
5 **DR. LISA BUTTERFIELD:** Thank you. And then
6 Dr. Maragh.
7 **DR. SAMANTHA MARAGH:** I just wanted to circle
8 back to the other comments, sort of expand my comments
9 on next-generation sequencing and concur with
10 everything that was said after me which is the
11 bioinformatics and the ability to analyze that data is
12 very problematic if you don't have a database that has
13 the information or the sequences that you want to
14 assess whether they're present in your sample.
15 So fundamentally, if the viral sequences that
16 you want to say are at least present were not in the
17 comparison bank that you were using, you're never going
18 to find them. And that can be an informatics problem
19 as opposed to a biochemistry assay capability problem.
20 It is solvable because, if you know the sequences like
21 Dr. Denner was showing, you can make G blocks and you

1 can have those sorts of controls and actually put them
2 in.
3 NIST has done some work in this space. If
4 that is an assay type, an application type that FDA
5 wants to be able to use and have sponsors leveraged,
6 then there are paths to make that more available for
7 this space. So I just wanted to bring that up and
8 absolutely second that (inaudible) problem is a
9 problem.
10 I suspect as Dr. Denner was saying that that
11 might fundamentally be the issue why other sequencing
12 applications may not have found something even if they
13 were expected or known to be present via other kinds of
14 assays because the database just didn't have the
15 information to say, yes, this is present. That is
16 truly a challenge that technology does want to be used
17 for this level of application.
18 **DR. LISA BUTTERFIELD:** Great. Thank you. All
19 right. So those are all of the comments and
20 discussion. It's been a lot of very active discussion,
21 a lot of participation, so thank you all for that.

1 So I think I'll go ahead and start to
2 summarize and then leave a few minutes for anything I
3 might have missed or people would also like to
4 emphasize.
5 So I think there's been a reiteration that we
6 do need these tissue banks. We need standardized
7 sample processing assay SOPs that take into account the
8 assays we want to perform with those samples and the
9 duration of this archiving.
10 There is certainly a role for RNA and DNA and
11 PCR or serological testing, and the data I think are
12 clear that the timing of which assays are performed on
13 what timepoint sample is very important and gives you
14 very important information. So that has to be
15 carefully considered as these things become more
16 standardized, young versus old animals for testing.
17 There is perhaps a role for consortia. We
18 heard in the Open Public Hearing from a representative
19 of a number of professional societies in
20 transplantation, and there might be a role there to
21 address some of these questions.

1 So thinking about these questions,
2 technologies, it looks like, as I said, DNA, RNA, PCR,
3 or serological testing, perhaps less of an emphasis
4 from the group on next-gen sequencing for perhaps more
5 sensitivity than is warranted at too great a cost and
6 with informatics limitations that were just
7 highlighted.
8 In terms of the timing, that a prescriptive 50
9 years is perhaps not required in all settings and what
10 one would do with a 50-year-old sample depending on the
11 situation is entirely unclear. The utility of those
12 samples seems to be (inaudible) than originally
13 thought.
14 So there's a place for one consortia
15 recommendations here in different settings but perhaps
16 more importantly a case-by-case discussion between
17 sponsors about the expectation for their target patient
18 populations and what makes the most sense and to have
19 that be an open discussion between the Agency and the
20 sponsors.
21 There's also room around the table for the

1 input of the patients and patient advocates.

2 In terms of discussion, conditions that would

3 alter the expectations for patient follow-up, certainly

4 any illness detected, any pathogen or new pathogen

5 detection would increase the expectations of patient

6 follow-up. There were I think too many unknowns for

7 any thought today to decrease the requirement for

8 patient follow-up.

9 Similarly, any conditions under which patient

10 follow-up for disease transmission should not be

11 required. Again, what I heard was still too many

12 unknowns and no suggestion of specific situations in

13 which follow-up would no longer be required.

14 I think donating blood and tissue or organs

15 sort of follows that. No one made any suggestions that

16 those requirements should be opened up although that

17 was not addressed well if follow-up for disease

18 transmission is not considered to be something with a

19 known end time. Perhaps those donations are also too

20 early to be considered given the unknowns about novel

21 pathogens and the state of the field in terms of the

1 human patient experience.

2 That's what I heard so I will look for hands

3 if anyone would like to emphasize something more or

4 less or add to what I summarized.

5 Seeing no hands, I will also ask regarding

6 Question 2 if anyone from the Agency would like to

7 weigh in with additional questions or if this was a

8 sufficient answer at this time for Question 2. I do

9 see Steven Bauer with a hand raised so, please.

10 **DR. STEVEN BAUER:** Can you see me and hear me?

11 **DR. LISA BUTTERFIELD:** Yes.

12 **DR. STEVEN BAUER:** Yeah, so most of this

13 conversation has been centered around the organ

14 transplant area. I just wanted to make a few comments.

15 I gave some thought around well-characterized cell

16 lines. So we do have this ex vivo scenario, the

17 various (audio skip) between the product and animal

18 cells, and, in that kind of scenario, we can fair quite

19 a sophisticated analytical technology, the very (audio

20 skip) cell base. So I just wanted to see if there were

21 any last thoughts from members of the Committee about

1 patients (audio skip) that we (audio skip) earlier with
2 regard to those kinds of products with (audio skip).
3 **DR. LISA BUTTERFIELD:** Thank you. So I'll
4 look for hands but what I -- my sense of the discussion
5 was that our ability to analyze those that you suggest
6 seems in hand, and the real crux of the discussion is
7 around the transplanted organs. But I'll look for
8 hands if anyone would like to add to the discussions
9 particular to ex vivo exposure to xenogeneic cell lines
10 that are characterized. Nothing to add.
11 **DR. STEVEN BAUER:** Thanks for that
12 consideration. Appreciate it.
13 **DR. LISA BUTTERFIELD:** Thank you. All right.
14 Then, if there are no comments from our Agency
15 colleagues about the discussion for Question 2, we are
16 a bit ahead of schedule, which is very nice, despite
17 all the robust discussion, and we now have a break that
18 was originally scheduled for ten minutes. I would like
19 to call 20 minutes for that break, and so why don't we
20 all come back. I have 12:06 in San Francisco so at
21 12:26 or 26 after the hour where you are. Thank you

1 very much.

2 **MR. MICHAEL KAWCZYNSKI:** All right. Twenty

3 minutes. I have set it so -- all right. We will

4 reconvene in 20 minutes. Studio, please take us to

5 break.

6 **[BREAK]**

7

8 **FDA TALK INTRODUCTORY TO CMC QUESTION 3**

9

10 **MR. MICHAEL KAWCZYNSKI:** All right. Welcome

11 back to our 73rd meeting of the Cellular, Tissue, Gene

12 Therapies Advisory Committee meeting with our chair,

13 Dr. Lisa Butterfield. Dr. Butterfield, are you ready?

14 **DR. LISA BUTTERFIELD:** Yes. All right.

15 Welcome back from that break, everyone, and now let's

16 move to the final question for today's discussion,

17 which is Question 3. So now we welcome Dr. Hursh from

18 OTAT to begin this section.

19 **DR. DEBORAH HURSH:** Thank you, Dr.

20 Butterfield, and good afternoon. I am Deborah Hursh,

21 and I'm a chemistry manufacturing in controls, also

1 known as product quality reviewer, in the Office of
2 Tissues and Advanced Therapies. I will briefly discuss
3 issues related to the requirements for the release of
4 biologic products.
5 Ms. Arcidiacono already gave you this
6 definition of xenotransplantation, but it is important
7 to note that most xenotransplantation products will be
8 medical products regulated as biologics and subject to
9 the General Biological Product Standards as outlined in
10 the Code of Federal Regulations. These are potency,
11 sterility, purity, and identity.
12 Potency is defined as in vitro or in vivo
13 tests specifically designed for each product. And the
14 word potency is interpreted to mean the capacity of the
15 product to effect a given result. It should be noted
16 that the ability of a test to demonstrate product
17 potency must be supported by data submitted by the
18 sponsor to the FDA.
19 Sterility testing of the final product is
20 required prior to administration to a human subject.
21 Sterility tests must be appropriate with the correct

1 sensitivity and specificity. Data documenting both
2 sensitivity and specificity will need to be summited to
3 the FDA in an IND prior to initiating a clinical study.
4 Sterility tests need to be validated to demonstrate
5 that the test is capable of reliably and consistently
6 detecting the presence of viable microorganisms.
7 The product should have tests that demonstrate
8 its identity. Such tests should demonstrate that it is
9 the correct product with the correct characteristics.
10 The method to demonstrate identity will be designed by
11 the product's manufacturer.
12 Finally, the Biologics Regulations say that
13 products must be pure, which means free of extraneous
14 material except that which is expected due to
15 manufacturing. This means testing and establishing
16 specifications for residual manufacturing material and
17 also pyrogenic substances, such as endotoxin.
18 For cellular xenotransplantation products,
19 this will be a more straightforward endeavor. Using
20 pancreatic islets as an example, potency might be a
21 test of insulin production connected to the number of

1 pancreatic beta cells to be administered.

2 It is important to note that the ability of

3 this to accurately predict product potency will need to

4 be supported by data. Identity could be a measure of

5 cell markers by a method such as flow cytometry or PCR.

6 Sterility, testing of residuals, and endotoxin testing

7 all have clear precedence in human somatic cell therapy

8 products that can be used as models.

9 However, for whole vascularized organs, things

10 are more complex. Human allogeneic organs are not

11 regulated by the FDA. They are regulated under the

12 Public Health Service Act through the Health Resources

13 and Service Administration, or HRSA. The test and

14 acceptance criteria are only broadly outlined under

15 regulation and the details worked out by individual

16 organ procurement transplant network members.

17 Here are some generalized types of tests for

18 human organs using the kidney as a model. The health

19 status of the donor, including the cause of death, and

20 pre-donation creatinine levels are assessed. There is

21 a macroscopic inspection of the organ and, in many but

1 not in all cases, a biopsy of the organ. The biopsy
2 system itself has limitations as a predictive
3 indicator.
4 There are other methods being investigated to
5 assess the donor kidney. Ex vivo perfusion
6 measurements, such as the Glomerular Filtration Rate,
7 renal blood flow, or intra-renal resistance may be
8 predictive of transplant success. Biomarkers of
9 perfusate that indicate organ health, such as lactate
10 dehydrogenase or Glutathione-S-transferase, are being
11 considered and, of course, new Omics approaches. The
12 transcriptomic descriptions of organs are being
13 investigated.
14 This is to point out that, while human
15 allogeneic kidney transplantation is an established
16 curative medical procedure, the current methods of
17 assessing organ function fall short of being fully
18 predictive of outcome. For xenotransplantation organs,
19 the risk calculus is very different because of the
20 uncertainty regarding their ability to sustain all
21 organ functions in the human recipient, persist through

1 the life span of the patient, and not transmit
2 unpredictable infectious agents.
3 Their status as biologics also requires that
4 these xenotransplantation organs be tested. There
5 needs to be pathogen testing, which will include
6 routine surveillance of the herd, testing the whole
7 animal prior to removal of the organ, testing the
8 organs or surrounding tissues, and provision for
9 retention samples. As xeno organs will come from
10 animals with intentional genetic alterations, there
11 will need to be verification of these alterations
12 immediately prior to removal from the animal and a
13 visual inspection of the organ at transplant, which
14 should include size matching.
15 Big organs have been known to increase in size
16 after transplant, which should also be taken into
17 consideration. Purity will include endotoxin testing
18 as well as tests in appropriate criteria for any
19 residual transport fluids. The most problematic issue
20 will be potency as this will not be limited to an
21 assessment of organ viability by a visual inspection.

1 But some assessment of organ function, either prior to
2 removal from the animal or ex vivo before transplanting
3 into a human subject. For all tests resulting to
4 safety, multiple time points will be required with
5 justification.
6 Given the complexities I have outlined, we
7 would like the Committee to discuss approaches to
8 predict transplant success in human subject safety
9 while also fulfilling expectations of compliance with
10 the regulations of biologics products. I thank you for
11 your attention, and I think I could take a couple brief
12 clarifying questions.
13
14 **Q&A SESSION**
15
16 **DR. LISA BUTTERFIELD:** Thank you very much,
17 Dr. Hursh. Yes, we definitely have plenty of time for
18 questions. Let's start with Dr. Ahsan, please.
19 **DR. TABASSUM AHSAN:** Dr. Hursh, thanks for
20 that presentation. That was really direct and to the
21 point, very helpful. Let me ask you a question because

1 I don't understand the historical perspective. Could
2 you tell me a little bit about decellularized SIS and
3 the release criteria related to that and how that may
4 play into what we're talking about today because
5 there's a long history there.
6 It is decellularized, so that is one separate
7 issue. But what has been the classic release testing
8 for that product or similar products?
9 **DR. DEBORAH HURSH:** Decellularized what? I
10 missed the noun.
11 **DR. TABASSUM AHSAN:** SIS, small intestinal
12 submucosa.
13 **DR. DEBORAH HURSH:** SIS?
14 **DR. TABASSUM AHSAN:** Yeah.
15 **DR. DEBORAH HURSH:** Oh, okay. I think those
16 are regulated as devices.
17 **DR. TABASSUM AHSAN:** Yeah.
18 **DR. DEBORAH HURSH:** Decellularized products
19 are often regulated as devices. They are subject to a
20 fully different set of regulations.
21 **DR. TABASSUM AHSAN:** Yeah. So that's my

1 concern. I do know that they are regulated out of a
2 510(k) mechanism. But the risks are the same that
3 we're trying to think about. Now, it is
4 decellularized, but we don't know to what level. So I
5 guess the question is, in these xenotransplantation,
6 are those definitely going to remain separate from what
7 we're talking about here?
8 **DR. DEBORAH HURSH:** Yeah.
9 **DR. TABASSUM AHSAN:** Is that the future?
10 **DR. DEBORAH HURSH:** Yes.
11 **DR. TABASSUM AHSAN:** Okay.
12 **DR. DEBORAH HURSH:** I would argue that the
13 risk for a decellularized product is significantly less
14 than the risk of a product with cells. That's why, A,
15 it's a device and, B, it can be even under the 510(k)
16 system.
17 **DR. TABASSUM AHSAN:** Okay. Great. Thanks for
18 that clarity.
19 **DR. LISA BUTTERFIELD:** Thank you. I guess, as
20 someone who's been a party to a number of cancer-
21 related cell therapy products, our guidance has always

1 been to begin to develop and think about the potency
2 assay because it has to be ready later on. As long as
3 you're always early stage, it's pretty minimal because
4 we're still learning. It's the first in human, and we
5 just don't have a lot of data.
6 In this setting, how would that be different
7 when we're really talking about a whole organ that has
8 to function and not a therapeutic that may or may not
9 show clinical efficacy in a patient?
10 **DR. DEBORAH HURSH:** Well, I think we've been
11 relatively flexible about this. I think the message we
12 would like to get across is that developers should be
13 making plans for this, and, in their pre-IND and IND
14 packages, they should have a proposal. They should not
15 assume that the rules for allotransplantation will
16 apply entirely here.
17 We will certainly leverage that information,
18 but we have regulations. So we'd like to see sponsors
19 proposing what they might do with the potency assay.
20 **DR. LISA BUTTERFIELD:** And then, I guess,
21 another question from me would be about identity. I'm

1 used to thinking about -- I have a cell population.
2 They are T cells. They are dendritic cells. So
3 identity is very straightforward. How has this been
4 approached in the solid organ multicellular, different
5 cell setting?
6 **DR. DEBORAH HURSH:** Well, that's the issue.
7 It hasn't been approached because these are
8 aspirational products. They're not on the ground yet.
9 I think the message, again, is that we would expect
10 some nucleic acid testing that you have that right
11 animal and that the animal has the correct
12 modification. There would be a host of tests, but it
13 wouldn't just be, oh, this is the pig with the right
14 tag on it. We would want to see something a little
15 more than that.
16 **DR. LISA BUTTERFIELD:** Thank you. Dr. Bloom
17 and then Dr. Fishman, please.
18 **DR. MARSHALL BLOOM:** Hi. Thanks for that nice
19 presentation. I just have one question about it, and I
20 forget the terminology used, like functionality or
21 something. I can see how you'd do that with a kidney

1 with, say, Glomerular Filtration or creatinine. And I
2 could see how you would do that with the pancreatic
3 cells, like insulin production. What would you use for
4 the heart, like ejection fraction or what?
5 **DR. DEBORAH HURSH:** Yeah. I think that we're
6 hoping that people will really use this as a chance to
7 develop imaging. There's a lot of imaging that's out
8 there that could be applied here. Certainly, ejection
9 fraction would be something that could be looked at in
10 the heart. We're hoping this will be a creative group.
11 They've been very creative making these pigs, so
12 hopefully, they'll be characterizing them. Imaging is
13 certainly something we're thinking about.
14 **DR. MARSHALL BLOOM:** Cool. Thanks a lot.
15 **DR. LISA BUTTERFIELD:** Thank you. Dr.
16 Fishman, your question.
17 **DR. JAY FISHMAN:** Thank you. That was a great
18 presentation and very instructive. I have a conceptual
19 problem, which probably wouldn't surprise you.
20 Transplanting an organ from a pig into a human requires
21 surgery, requires immunosuppression. It's kind of a

1 package deal. So we would assume that the heart would
2 work in the pig, but we have no way of knowing if it's
3 going to work in the human.
4 It's not going to work independent of the
5 immune suppression or the infectious risk at the result
6 of the immune suppression. So the concept is very
7 good. You described it all very well. But I'm not
8 sure how you describe the package because what was just
9 asked is do we have to put it into a person to show
10 that it works and meets your criteria?
11 **DR. DEBORAH HURSH:** Dr. Fishman, that's
12 actually generic to all of this. The standards require
13 us to assess the product before it goes in the patient.
14 But how the product performs in the patient is part of
15 the clinical study, and that's no different for
16 hematopoietic stem cells than it is for this. I think
17 that we see it -- it is a package deal. We agree with
18 you.
19 But the Biologics Standards require us to have
20 an assessment that the product is of the correct
21 identity and high quality prior to going in. From

1 there, it's part of the clinical study.

2 **DR. JAY FISHMAN:** Thanks.

3 **DR. LISA BUTTERFIELD:** Okay. Any other

4 questions for Dr. Hursh before we start the Committee-

5 wide discussion? Dr. Zeiss, please.

6 **DR. CAROLINE ZEISS:** Hi, Dr. Hursh. Regarding

7 function as a measure of potency, do you think there's

8 anything to be gained to assess function ex vivo

9 between removing it from the pig and putting the organ

10 into a person?

11 **DR. DEBORAH HURSH:** Yeah.

12 **DR. CAROLINE ZEISS:** Are we sure that -- okay.

13 However, that could have a downside of the --

14 **DR. DEBORAH HURSH:** Yeah. I think that is

15 something people are considering from my reading of the

16 literature in this area because sometimes they're put

17 on these machines -- we'll stay with the kidney -- to

18 keep them perfused. That's something people are

19 considering. I don't think we have an answer, which is

20 why we're asking all of you.

21 **DR. CAROLINE ZEISS:** Okay. Thank you.

1 **DR. LISA BUTTERFIELD:** All right. Thank you
2 again, Dr. Hursh. This leads us, then, to the
3 Committee-wide discussion for Question 3. We've seen
4 Question 3 posted up.
5 Pig cells or organs transplanted into humans
6 are FDA-regulated articles and are subject to
7 regulatory requirements such as identity, purity, and
8 potency.
9 So we are charged with discussing assays or
10 testing strategies that might be appropriate to perform
11 prior to transplantation to evaluate safety and
12 efficacy of these articles. To get us rolling, our
13 discussant is Dr. Ahsan.
14 **MR. MICHAEL KAWCZYNSKI:** Sorry. What was the
15 name of that one? I apologize. I didn't hear.
16 **DR. LISA BUTTERFIELD:** Dr. Ahsan, Taby Ahsan.
17 **MR. MICHAEL KAWCZYNSKI:** If you could raise
18 your hand, that would help a second. There you are.
19 Thank you. Perfect. All right. My bad.
20

1 **COMMITTEE DISCUSSION OF QUESTION #3**

2

3 **DR. TABASSUM AHSAN:** No worries. We're
4 getting to the end of a long day. I wanted to talk a
5 little bit about this question as it has been posed.
6 One thing is the question is actually focused on safety
7 and efficacy, and not identity and purity. There is
8 quite a bit to be discussed on identity and purity. I
9 think Dr. Butterfield brought it up a little bit as
10 well. I think, since the question really focuses on
11 the latter two, I'll start primarily with that.
12 As we've kind of discussed,
13 xenotransplantation covers a product range that is very
14 broad, from cell lines all the way to whole organs. So
15 it's really not appropriate to think of a single
16 solution and to apply that to all the scenarios, right?
17 So I do think that we are in early stages, and, as Dr.
18 Hursh said, these are aspirational products. So we
19 need to think about having a lot of interact meetings
20 and pre-IND discussions and then continued discussions
21 after the IND to really understand how we're going to

1 formulate a more not standard but consistent
2 expectation of what kind of release testing we'll need
3 for these.
4 Let's first talk about safety. Safety, of
5 course, always starts with some sort of macroscopic
6 evaluation, whether it's cell populations and you're
7 just looking at morphology or if you're going to look
8 at the whole organ. I'm also not going to focus really
9 on a fungal or bacterial testing. Those are fairly
10 standard for sterility and mycoplasma testing.
11 I will say that the briefing document as well
12 as the guidance talk about endotoxin testing and that
13 being a requirement. And I can't see a reason why not
14 to do that, so I think that that's a reasonable
15 expectation to continue.
16 Today, we've really focused on infectious
17 agents. So let me talk a little bit about that and how
18 we might think about that. I do think, even in the
19 discussion, we need to stratify the product so we can
20 think separately about the whole organ versus the cell
21 lines. I think Dr. Breuer brought up the cell lines

1 because he thought it was being a little bit
2 underdiscussed, but I'll try to discuss both of them.
3 Let me first start with the organ
4 transplantation just to contradict what I just said a
5 moment ago. In organ transplantation, the testing that
6 we would expect on the organ itself cannot be conducted
7 where the results are returned in time for
8 transplantation.
9 We touched upon it earlier this morning, but
10 it says one of the focuses is on herd management and
11 animal screening. So there was a lot of good
12 presentations earlier today on that. So when we think
13 about the herd management, I think Dr. Denner brought
14 up no viral load versus low viral load in animals. I
15 think the utility of that very much depends on the
16 urgency of the need for the organ and how you relate
17 that benefit-to-risk ratio.
18 But it always concerns me with words like
19 "low" and "high" because what is "low"? How do we set
20 that threshold? What do we know that to be? I think
21 this is a space where, again, in the absence of

1 knowledge or understanding, we really need to create
2 knowledge and data. So tracking that information as we
3 move forward I think is a really important part. But
4 that wouldn't be part of the release testing. That's
5 part of the process. So that'll be somewhere else in
6 IND in terms of release then.
7 Now, another question to think about, which
8 Dr. Denner touched upon too, which is, where do we take
9 the samples for testing from the animals? Dr. Denner
10 very nicely laid out kind of a schema for the
11 simultaneous detection of different viruses. But
12 another way to also show was that there was data
13 presented that the biodistribution of viruses and
14 stuff, the various organs and tissues in the body, is
15 not consistent.
16 So if we think that for a given virus that
17 that is not consistent, it's likely that for multiple
18 viruses it is not the same. So on a virus-by-virus
19 basis, we may need to think about where we source the
20 samples for which we test in these animals when we do
21 the screening. It might be other organs. Sometimes

1 it's the organ itself in terms of a biopsy. And
2 sometimes it may be the adjacent tissues.
3 That, again, I think is very difficult and
4 challenging to be prescriptive about that in advance.
5 I think we need to have those discussions and think on
6 an application-by-application basis, which organ are we
7 talking about, in terms of how we would test. And then
8 we may have to test separate samples for the different
9 viruses and to think of it that way.
10 Now, let me switch a little bit to cells and
11 tissues. This, as Dr. Butterfield mentioned, is very
12 in line with the cell therapies, whether we're talking
13 about immunotherapies or stem cell therapies that are
14 emerging. So aligning ourselves in the xeno space with
15 those fields I think makes a lot of sense. One of the
16 things to think about, then, is what are the other
17 guidances saying as to safety? Of course, they have
18 very prescribed sterility and mico and endo testing and
19 the rest of it.
20 One of the things to also think about is, when
21 we do the virus testing, which is a very standard set

1 of tests that you would do, let's say, for an
2 allogeneic cell product, I think that that would apply
3 here too. But what we talked about earlier today was
4 that both PCR and serological assessments can be very
5 useful. So what we need is a matrix approach. And
6 that's been utilized, I think, in the cell therapy
7 field for quite a while.
8 We do primer-based PCR assessments, but we
9 also do in vitro and in vivo adventitious agent
10 testing, TEM testing, to try to capture those things
11 where, with quantitative PCR, with primer-based PCR,
12 you're asking a very specific question, and you get a
13 very specific answer. Maybe things like with -- not
14 maybe, definitely with tests like TEM and the
15 adventitious agent test, you're looking more broadly at
16 is there something that is worth looking at more
17 carefully. Subsequently, that does lead to additional
18 tests afterwards.
19 So I think a combination of those is very
20 important. Taking a matrix-based approach to viral
21 testing is, I think, what we have been doing in the

1 cell field for a while and would be important to
2 continue to do in the xeno space as well.
3 The other thing to think about is that assays
4 need to be sensitive, reproducible, but also
5 meaningful. There was some discussion about the
6 genomic assessments. The sensitivity with droplet
7 digital PCR is going up relative to quantitative PCR,
8 real-time PCR -- well, maybe not the sensitivity but
9 the reproducibility -- which gives you a lower LOQ and
10 an LOD. One of the questions we have to think about is
11 that we don't really have an understanding on the viral
12 load that leads to infectivity of human tissues. So
13 there's a lot of discussion into whether there is even
14 infectivity of human tissues.
15 We haven't seen a lot of correlation between
16 viral load and that response mostly because we haven't
17 been seeing infectivity. But what I do want to be
18 careful about is that, if we start developing these
19 genomic tools that are highly sensitive, that we end up
20 with essentially positive viral loads but they're not
21 biologically meaningful. Now, I do understand that

1 there was some data that was showing that, in the
2 explant organ, the viral load can go up over time.
3 So we do want to be sensitive to that. But we
4 do want to make sure that the assays that we're doing
5 are meaningful in terms of the biological response that
6 we're trying to capture. We have to have a balance in
7 terms of our interpretation of data.
8 This goes a little bit against what many
9 sponsors do. I'm a big fan of being generous in data
10 collection and then conservative in data
11 interpretation. But I think a lot of sponsors are very
12 wary of that, concerned that they're going to generate
13 data that will shoot themselves in the foot or
14 jeopardize their position. Somehow, we need to make
15 sure that that type of deeper product characterization
16 that we really need in these nascent fields is not
17 somehow disincentivized for the sponsor.
18 Then again, when you think about NGS and PCR
19 and TEM, there's a lot of different technologies and
20 emerging technologies of how we can get to genomic data
21 more specifically. Some of them are discovery

1 oriented. Some of them are question-answer oriented,
2 like real-time PCR. We want to use all of those tools.
3 Again, it's hard to prescribe without a specific
4 indication, without a specific approach of cells or
5 organs, how you should move forward.
6 But I think that these are the things that
7 need to be considered and discussed. So it's perhaps
8 more important to think about the issues that need to
9 be discussed pre-IND than actually the answers that
10 would be assigned to those questions.
11 In terms of, also, one other point about data
12 generation at this early level, the report results, the
13 for information only, the product characterization data
14 is hugely important, I think, not only on the
15 infectious viruses, but then that leads me to the
16 efficacy.
17 First, I like to separate efficacy versus
18 potency. Potency is the regulatory word. I think of
19 efficacy as the clinical outcomes. So what we're
20 thinking about here is what kind of potency tests are
21 we going to do. This is a major topic in biologic

1 products and viable products like CAR T and the rest of
2 the cell therapies. It really is an issue. We've seen
3 that in the last year or two that potency is a major
4 point of concern for many of these products going in
5 front of the FDA. Again, we need to take a matrix view
6 so that we can be more exploratory.
7 At these early-stage trials, that's when we
8 need to allow for larger product characterization with
9 many more assessments because we don't even know what
10 assay we will want to use for potency at this stage.
11 By the time we know or the time we need it, it'll be
12 too late to have generated the data to know. So we
13 really need to incentivize people to take that matrix
14 approach to potency assays, which many people have been
15 talking about, and try to then cull and narrow in on
16 the specific assays that are going to be valuable as
17 you advance your products through the different phase
18 trial.
19 We want to also think of potency assays as
20 crossing scale, RNA, protein, (inaudible), function,
21 all of those levels, not just a home run hit on a cell

1 function assay without any kind of supporting data.

2 Now, on the whole organ side, as was brought

3 up before, this is really challenging. How do we think

4 about potency in the organ once you've taken it out of

5 the body? And I think here this is a really important

6 question not only for xenotransplantation but because

7 organ engineering is emerging.

8 As we've graduated from tissue engineering to

9 organ engineering, we need to start thinking about

10 those potency assays in a more imaginative way. These

11 assays need to be developed. They might be imaging-

12 based. They might be some functional tests where you

13 actually attach the various interfaces of the organ and

14 see how it can function. For something like a lung, it

15 might be oxygen exchange. For the kidney, I think Dr.

16 Hursh gave some presentation for cardiomyocytes.

17 For a heart, it might be about some electrical

18 signal propagation and contraction and ejection volume.

19 There's a lot of things to think about. These are

20 really challenging questions when we get to the organ

21 level of how we think about functionality in vitro. So

1 I'll leave it with that. A lot more things to think
2 about and to question than answers that we can provide.
3 But I think it's an exciting time to generate
4 the data to help us target the future in terms of
5 evaluating answers to these regulatory issues that need
6 to be addressed.
7 **DR. LISA BUTTERFIELD:** Thank you very much,
8 Dr. Ahsan. That gets us started, and we do have a rare
9 opportunity here to impact CMC discussion. I'm now
10 opening this up to the Committee members and temporary
11 members. Let's start with Dr. Fishman, please.
12 **DR. JAY FISHMAN:** I'm fairly new to this, but
13 I don't know if I'm allowed to ask the question I'm
14 about to ask which is -- I think the presentations have
15 been great, by the way. Identity, purity, and potency,
16 if we apply this, which we're not allowed to do, to
17 human allotransplantation, we are putting organs into
18 people that we know are likely to be infected with
19 various pathogens that can kill the host -- my daily
20 bread and butter.
21 So I would call that acceptable risk. So I

1 wonder if there doesn't need to be a bar which says all
2 of what's just been said is completely accurate, but,
3 should the acceptable risk be extended beyond what we
4 accept in human allotransplantation in clinical
5 practice right now? I think there's an answer to that
6 which is that acceptable risk is defined by eventually
7 learning what those risks are by doing all the things
8 that we've talked about including clinical trials.
9 But this is an opportunity. In part, it's an
10 opportunity because pigs do not seem to be susceptible
11 to some of the common infectious agents to which human
12 organs are susceptible. I would point to HIV,
13 hepatitis B, and hepatitis C. So we may be starting
14 out from a better place, and then we have the
15 opportunity, for example, to immunosuppress these donor
16 animals and see what pops up. We don't do any of that
17 with human organs.
18 We do a social and epidemiologic discussion.
19 We often have wrong data. We ask family members, "Has
20 your family member, your loved one, ever used drugs or
21 ever been in a bad place or et cetera," and we get

1 answers that we know on their face are incorrect. So
2 our screening methodology for human allotransplantation
3 is flawed. We know that. We have some good tests. We
4 have some serologic tests and nucleic acid tests that
5 we do.
6 But I just wonder if we should think
7 preclinical testing for sure. We can immunosuppress
8 animals. We can do a variety of things. But should
9 that bar be higher for xenotransplant, in terms of
10 acceptable risk, than it is for allotransplant?
11 Thanks.
12 **DR. LISA BUTTERFIELD:** Thank you for the
13 provocative comments. Next is Dr. Morrison and then
14 back to Dr. Ahsan.
15 **DR. SEAN MORRISON:** I don't want to sidetrack
16 the discussion that we're having, but I wanted to bring
17 up an issue that's related to probably all of the
18 questions that we've had today and that hasn't been
19 discussed. And that is the issue of international
20 harmonization. I'm sure this is something that the FDA
21 hears about a lot, but it's just worth noting briefly

1 that it creates a really difficult situation when the
2 regulations in different countries, with respect to
3 exposure to xenogeneic cell lines, are different in a
4 way.

5 For some of these things, the differences
6 might be modest enough that it would be slightly
7 different testing requirements in different places.
8 But, for some of these regulations, it could create a
9 situation in which different products have to be
10 designed to be marketed in Europe versus the United
11 States versus Australia. To the extent that it's
12 possible, it's worth the FDA conferring with their
13 colleagues in other countries to try to harmonize
14 whatever comes out of this as best they can.

15 **DR. LISA BUTTERFIELD:** I'd like to suggest and
16 follow up that perhaps the lack of harmonization in the
17 early stages gives us a broader opportunity to learn
18 what works and what doesn't, what does predict efficacy
19 and what doesn't, to be followed by international
20 harmonization.

21 **DR. SEAN MORRISON:** Yes, good point.

1 **DR. LISA BUTTERFIELD:** Thank you, Dr.
2 Morrison. Dr. Ahsan and then Dr. Zeiss.
3 **DR. TABASSUM AHSAN:** Thanks. I wanted to
4 actually touch on Dr. Fishman's point about higher
5 expectations of the xenotransplantation field than
6 there is of the human organ transplantation and then
7 maybe the cell therapy. I think that that's something
8 that I completely agree with, that we need to align
9 those aspects.
10 For sure, in CMC production of cell therapies,
11 there are many cell therapies that the process involves
12 xenogeneic factors, whether it's SBS, which has been
13 very classic, trypsin, which is porcine, some mouse
14 monoclonal antibodies, et cetera, for sorting or what
15 not. So trying to align the testing with the risk I
16 think is really important. There's different levels of
17 risk in all of this.
18 So I think that that's something that we
19 really want to right-size because I don't think we want
20 to carry from one field to another testing panels
21 without evaluating the changes in risk. Now, I think,

1 if I understand this correctly, I mean, part of the
2 issue with the infectious viruses on the porcine
3 material versus the human transplant material is that
4 we're afraid of introducing new viruses to which we
5 have no treatments and that we can spread that through
6 the public domain.
7 So I think that that's why the testing
8 paradigm of the tissue, the patient, the patient's
9 close contacts is part of the paradigm. I think that
10 there's going to be discussion tomorrow about that, and
11 we can talk about that more in depth.
12 We do have, sometimes, passed along precedent
13 without passing along the historical justification for
14 that precedent. So I just want to make sure that, as
15 we try to align the different fields, that we do think
16 about the relative risk and right-size the release
17 panels to that risk.
18 **DR. LISA BUTTERFIELD:** Great. Thank you. Dr.
19 Zeiss.
20 **DR. CAROLINE ZEISS:** Just a question. I do
21 agree that, on the infectious disease front, there are

1 so many unknowns that all caution is indicated there.
2 However, on the functional front, if we consider what
3 it would take to do ex vivo functional testing after
4 removal of the organ from the donor, do we really gain
5 anything with the cruxes downstream from that, in other
6 words, putting the organ into the recipient? Do we
7 really need to have higher standards for
8 xenotransplanted organs than allogeneic organs? The
9 consequence of doing these functional tests is to
10 increase time outside of the donor, and that could have
11 negative consequences. Thank you.
12 **DR. LISA BUTTERFIELD:** Thank you. Dr. Kimmel
13 and then Dr. Palevsky. Not hearing you yet, Dr.
14 Kimmel.
15 **MR. MICHAEL KAWCZYNSKI:** Your phone's muted,
16 sir. Let's see. Your headset's connected.
17 **DR. PAUL KIMMEL:** How about now?
18 **MR. MICHAEL KAWCZYNSKI:** There we go.
19 **DR. PAUL KIMMEL:** Great. Thank you. I think
20 I have a corollary question to Dr. Zeiss', and again
21 potency is a new concept for me. But I was thinking,

1 if a approach to the evaluation of the organ before
2 transplantation should be similar to what we do in
3 kidney transplantation, which I'm more familiar with
4 than heart transplantation, the standard should be that
5 the GFR is equivalent to a normal level within a pig.
6 That would ensure that there is a level of
7 function available. And I think there should be a
8 minimum standard on that, which probably has to be
9 normalized to age and size and weight and also that
10 there's no protein excretion, suggesting that there's
11 no disease of the kidney.
12 Often, before transplantation, there's a
13 biopsy that's done, and it's quickly read. I'm sort of
14 agreeing with Dr. Zeiss, that we don't often do an ex
15 vivo measurement of the kidney function before
16 transplantation because it doesn't really tell us that
17 much more than what we know is happening in the living
18 donor. Those were my viewpoints.
19 **DR. LISA BUTTERFIELD:** Thank you. Dr.
20 Palevsky.
21 **DR. PAUL PALEVSKY:** For some reason, my camera

1 isn't --

2 **DR. LISA BUTTERFIELD:** We hear you.

3 **DR. PAUL PALEVSKY:** Okay. My comments were

4 going to be very similar to what Dr. Kimmel just

5 expressed. In talking about potency, my concept is

6 really talking about it in terms of organ function,

7 which can be assessed in the animal before the organ is

8 harvested, as Dr. Kimmel expressed, looking for the

9 kidney GFR and urine albumin excretion. I'd also want

10 to have some standard in terms of anatomy, both in

11 terms of organ size, vascular structure, ureteral

12 structure, that all of those would be normal.

13 Analogous I guess for the heart would be the structural

14 integrity of the heart and the function.

15 Moving back a step, the discussion so far in

16 terms of identity and purity has focused on the

17 identification of viruses. But as I think we'll be

18 hearing about tomorrow, these animals are going to be

19 genetically modified to minimize the risk of rejection.

20 We need to have a standard to ensure that the organs,

21 as they're being used, actually have all the genetic

1 modifications that are specified.

2 So how is that going to be tested? Is that
3 going to be accepted just based on the breeding of the
4 animal? Or is that going to actually require testing
5 of the animal before the organ would be able to be
6 taken for use?

7 **DR. LISA BUTTERFIELD:** Thank you. Dr. Cooper,
8 I saw your hand up earlier. I see it down, so please
9 put your hand back up if you wanted to add something.
10 Then I'll ask in general, other Committee members, if
11 you also want to add something. Why don't we move back
12 to Dr. Morrison.

13 **DR. SEAN MORRISON:** Hey there. One other
14 orthogonal point, and that is that, if we get to the
15 point where there are genetically engineered pigs and
16 where there's evidence that xenografting is actually
17 effective at some level for organs, we could end up
18 also having a situation where there are either unproven
19 therapies or xenograft tourism, much as there has been
20 stem cell unproven therapies and stem cell tourism now.

21 I'm not talking about organ transplants. I'm

1 talking about what if people start getting injections
2 of genetically-engineered pig chondrocytes in their
3 knees, for example, either at unproven therapies in the
4 U.S. or in other countries to the extent that we
5 believe that xenografts offer the risk of a public
6 health problem, the result of new pathogens traveling
7 into the human population. We should just have that on
8 our radar screen.
9 As crazy as it may sound, it's worth bearing
10 in mind that people already get injections of
11 allogeneic products that are destroyed within days of
12 injection in their body. But they still come to
13 believe that those products offer the potential for
14 long-term health benefits. So it's not much of a leap
15 from the exosome therapies and allogeneic cell
16 therapies that people currently get to the idea of a
17 xenogeneic therapy if xenogeneic therapies get some
18 public traction in terms of utility in some other
19 context.
20 So, if we believe that there's a potential
21 public health problem in this, then we have to be ready

1 to react if we start having significant -- does the FDA
2 regulate unproven xenogeneic therapies in a more
3 aggressive manner than non-xenogeneic unproven
4 therapies? And what happens if we have xenotransplant
5 tourism? I'll leave it there. Thanks.
6 **DR. LISA BUTTERFIELD:** Thank you. All right.
7 Again, our discussion question on what assays and
8 testing strategies we should be using for safety and
9 efficacy of these xeno cells and tissues. Other
10 thoughts from the Committee? If not, I'll take my
11 first stab at summing up the discussion we've had so
12 far on this question, and then we'll have a little time
13 left to see if people want to add after that.
14 All right, so I'll carry on. We've got a lot
15 of opportunities for safety, and there was agreement
16 with maintaining endotoxin. Thinking about pathogens,
17 we've had a lot of discussion earlier today about the
18 possible approaches for testing those. We need to
19 consider some of the complexity there of what assays
20 are performed in what organs given that different
21 viruses can infect different organs in the donor animal

1 differently. Would that be a biopsy of the organ to be
2 transplanted, or would adjacent tissues be acceptable?
3 That really is yet to be determined.
4 Herd management has been discussed, and this
5 is certainly an important aspect to make sure we have
6 correct animals, the expected genetic modifications, as
7 well as tracking and known exposures for those animals.
8 A notion that they could be immunosuppressed at some
9 stage to look for donor immune-suppressed reactivities
10 and pathogens.
11 Let's see. I've talked about organ biopsies.
12 We've discussed starting from the existing allo human
13 organ transplant regulations and then modifying those,
14 keeping in mind the clinical needs, the knowledge of
15 pathogens, changing the bar on acceptable risk, and
16 keeping in mind that a xeno organ might, as we learn
17 more, become safer than an allogeneic human organ
18 because of the differences in infectivity of the
19 viruses that are known to be in those animals.
20 Thinking about efficacy, it is still very
21 early. There was a call to start more broad and

1 somewhat exploratory assessments because we don't know
2 what assays are going to correlate with in vivo
3 efficacy for the recipient patient. We have to keep in
4 mind there are some existing fairly straightforward
5 functional tests for organs, insulin secretion,
6 pancreas, creatin infiltration in the kidney, ejection
7 fraction, electrical signaling in the heart, oxygen
8 exchange in the lungs.
9 But to minimize the notion that those would be
10 done ex vivo after removal because that could certainly
11 negatively affect downstream efficacy and to focus more
12 on in vivo donor testing of those functions and their
13 anatomy.
14 Then, we can consider imaging options, as
15 well, for some of these efficacy measures. And then,
16 certainly, the notion of harmonization across
17 international lines. And that has impact in a number
18 of ways, one, we should learn from each other and what
19 each country starts out with regulation to then
20 harmonize and make sure that everyone is following best
21 practices, and two, reduce chance of transplant tourism

1 where less regulated countries without harmonized
2 standards could be doing things that others know are
3 dangerous, and also, even within the U.S., tracking
4 unproven therapies, as we've seen happen with unproven
5 stem cell therapy.
6 So those are the themes I heard. I will watch
7 for hands to see if there's anything else that we'd
8 like to raise. Let me circle back to Dr. Hursh,
9 please.
10 **DR. DEBORAH HURSH:** Am I unmuted? Can you
11 hear me?
12 **DR. LISA BUTTERFIELD:** I hear you.
13 **DR. DEBORAH HURSH:** Yeah. Okay. There's a
14 lag. I just wanted to follow up on a couple of points,
15 particularly those raised by Dr. Zeiss.
16 It's not like we have a choice here. It's not
17 that we set out to regulate allo products different
18 than xeno products. It's the way the regulations are
19 set up, and the FDA has to obey its own regulations.
20 So we're trying to figure out how to apply this in a
21 way that does not set the field back. So that's point

1 one.

2 Her second point is that we have no intention

3 of holding these organs longer than they need to be

4 held, which is why I think imaging is a modality we're

5 going to want to look at. A lot of our products are

6 very, very short-lived, and we're used to thinking in

7 terms of trying to get assays that are done either

8 super quickly or done prior to removal.

9 So I just wanted to make those points. And

10 then I'm going to let Judy talk.

11 **DR. LISA BUTTERFIELD:** Thank you. Judy, would

12 you like to add?

13 **DR. JUDITH ARCIDIACONO:** And I unmuted?

14 **DR. LISA BUTTERFIELD:** Yes, I hear you.

15 **DR. JUDITH ARCIDIACONO:** Okay. So I just

16 wanted to clarify on the harmonization situation.

17 Probably for the past ten years or so, FDA has been

18 working with the International Xenotransplantation

19 Association and the World Health Organization on

20 policies for xenotransplantation, and 2019 was the last

21 time we met. The document is called the Changsha

1 Communique.

2 It is a commentary on international

3 harmonization of xenotransplantation regulations. At

4 that particular meeting, they adopted the U.S.

5 definition of xenotransplantation and also accepted

6 most of the recommendations in the 2016

7 Xenotransplantation Guidance.

8 Tourism, our other regulatory partners can't

9 really control that. That's always going to happen.

10 But there is a harmonized approach for regulatory

11 oversight. Just wanted to mention that.

12 **DR. LISA BUTTERFIELD:** Great. Thank you very

13 much. Okay, watching for other comments to add to the

14 summary of the discussion for Question 3. I will also

15 check in with Dr. Bryan to see if there are other

16 things from the Agency that they would like to hear

17 before we close out Question 3.

18 **DR. WILSON BRYAN:** Thank you, Dr. Butterfield.

19 No, I think the discussion today on all three questions

20 has been excellent. So I think we're in good shape.

21 Appreciate it.

1 **DR. LISA BUTTERFIELD:** All right. Thank you
2 so much, Dr. Bryan. With that, I believe we've managed
3 to have a terrific discussion with a lot of
4 participation across great expertise over today. While
5 we could continue talking, we still have tomorrow. So
6 I will turn this back to Christina Vert to close out
7 today.
8
9 **ADJOURNMENT**
10
11 **MS. CHRISTINA VERT:** Thank you, Dr.
12 Butterfield. Yes, I think this was a great first day.
13 We're also looking forward to the discussions tomorrow.
14 With that, I will formally adjourn the meeting for
15 today at 4:21 p.m. Eastern Daylight Time.
16 **MR. MICHAEL KAWCZYNSKI:** All right. Thank you
17 all. With that, studio, if you wouldn't mind, please
18 kill our feed. See you all tomorrow.
19
20 **[MEETING ADJOURNED FOR THE DAY]**