Food and Drug Administration
Center for Biologics Evaluation and Research
Summary Minutes
73rd Cellular, Tissue and Gene Therapies Advisory Committee Meeting
June 29-30, 2022

Committee Members Lisa Butterfield, Ph.D. (Chair) Tabassum Ahsan, Ph.D. Marshall Bloom, M.D. Christopher Breuer, M.D.+ Bernard Fox, Ph.D. Jeannette Yen Lee, Ph.D. Sean Morrison, Ph.D. Melanie Ott, Ph.D.+ Nirali Shah, M.D., MHSc.+ Gil Wolfe, M.D.+ Joseph Wu, M.D., Ph.D. **Temporary Voting Members** Hugh Auchincloss, M.D. Sridhar Basavaraju, M.D. Paul T. Conway> Matthew Cooper, M.D. Jay Fishman, M.D. Paul Kimmel, M.D., M.A.C.P., F.A.S.N. Samantha Maragh, Ph.D. Paul Palevsky, M.D. Caroline Zeiss, BVSc, Dip. A.C.V.P. & A.C.L.A.M., Ph.D. **Industry Representative** Eric Crombez, M.D. < **Consumer Representative** Kathleen O'Sullivan-Fortin** +Not Attending ** Consumer Representative *** Industry Representative <Alternate Industry Representative >Patient Representative	**Speakers and Guest Speakers** Joachim Denner, Dir.u. Prof.a.D. Kristi Helke, D.V.M., Ph.D., DACVP. Richard Pierson, III, M.D. Eckhard Wolf, Dr. med. vet **FDA Participants** Judith Arcidiacono, M.S. (Speaker) Steven Bauer, Ph.D. Patricia Beaston, M.D., Ph.D. (Speaker) Wilson Bryan, M.D. (Speaker) Deborah Hursh, Ph.D. (Speaker) Peter Marks, M.D., Ph.D. Steven Oh, Ph.D. Tejashri Purohit-Sheth, M.D. **Designated Federal Officers (DFO)** Christina Vert, M.S. Sussan Paydar, Ph.D. **Committee Management Officer (CMO)** Joanne Lipkind, M.S. **Committee Management Specialist (CMS)** Tonica Burke, B.S. **Director** Prabhakara Atreya, Ph.D.

These summary minutes for the June 29-30, 2022, meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee were approved on August 11, 2022.

I certify that I participated in the June 29-30, 2022, meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) meeting and that these minutes

accurately reflect what transpired.

/S/
Christina Vert, M.S.
Designated Federal Officer

/S/
Lisa H. Butterfield, Ph.D.
Chair

On June 29-30, 2022, at 10:00 a.m. Eastern Daylight Time (EDT), the 73rd meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) took place in open session to discuss regulatory expectations for xenotransplantation products. The discussion topics included human cells that have had ex vivo contact with animal cells, and animal organs and cells for transplantation into human subjects, both of which are xenotransplantation products. Given the topic of this meeting, it was determined to be a Particular Matter of General Applicability (PMGA).

On Day 1, June 29, Dr. Lisa Butterfield, the Chair, called the meeting to order. The DFO, Ms. Christina Vert, made administrative remarks, conducted roll call, and invited the committee members to introduce themselves, and read the Conflict of Interest (COI) statement into the public record. There were no conflict-of-interest waivers issued under 18 U.S. Code Section 208 in connection with this meeting. During the open session, CTGTAC members, consultants, FDA speakers, Guest Speakers, staff, and the public speakers all participated via the Adobe Connect web conference.

Dr. Wilson Bryan, Director of the Office of Tissues and Advanced Therapies, provided FDA Opening Remarks. This was followed by a presentation from the FDA Speaker, Ms. Judith Arcidiacono, on "FDA Views on Xenotransplantation." Immediately following this presentation, there was a 10-minute Q & A session for the FDA Speaker.

Following the FDA Q&A, Session 1 on "Human Cells That Have Ex Vivo Contact with Animal Cells" commenced. For the start of Session 1, the Guest Speaker, Dr. Joachim Denner, gave a presentation on "Emerging Zoonotic Diseases." Immediately following the presentation, there was a 10-minute Q & A session for Dr. Denner.

During the start of Committee Discussion of Questions for Session 1, the following discussion question was presented to the Committee:

Discussion Question #1:

1. Pigs can harbor endogenous viruses that may impact the health of transplanted tissues or organs or impart infectious disease risk to the recipient and their close contacts. Porcine circovirus 3 (PCV 3), porcine endogenous retrovirus (PERV) and porcine cytomegalovirus (PCMV) have been identified as viruses that may impact organ function after transplantation or be transmitted to recipients of xenotransplantation products,

their contacts, and the public. Please discuss the following:

a. Describe sensitive detection systems available for the detection of infectious agents in pigs used for xenotransplantation, and which methods should be used orthogonally.

b. PCV 3 transmission from donor pigs to baboons has been reported in preclinical studies. Please discuss the potential for PCV 3 xenozoonotic infections in humans.

c. PCV 3-infected pigs have been reported to exhibit cardiac and multisystemic inflammation. Please discuss the impact of PCV 3 on transplanted organs.

d. Three subtypes of PERV (A, B, C) and PERV A/C recombinants have been found in various breeds of pigs. Please discuss which subtypes present the greatest risk and how PERV risk can be mitigated or eliminated.

e. Please discuss any other known or emerging viruses that should be considered in the context of human xenotransplantation.

Summary of Discussion: *The committee discussed the multiple known porcine viruses that impact organ function, directly cause disease in humans, or may cause complications, such as coagulopathy in humans. There were discussions of the need to identify or develop tests for specific viruses, although no single platform exists to test for all of the diseases mentioned. The committee noted that while many porcine viruses have not been shown to infect normal healthy human cells, the recipient of a xenotransplantation product will be immune-compromised or immune-suppressed, so that current data may not be representative of transplant conditions.* The committee discussed patient monitoring and recommended that testing be performed frequently immediately after transplant and tapering off over time.

After the discussion of Question #1, the Committee went to lunch. Once the Committee returned from lunch, a 25-minute Open Public Hearing (OPH) session was held from 1:15 p.m. to 1:40 p.m. in which two pre-registered public speakers provided presentations. The names of OPH speakers and their remarks may be obtained from the transcript posted on the website.

Following the OPH session, the Guest Speaker, Dr. Joachim Denner, gave a second presentation on "Methods for the Detection of Infectious Diseases." Immediately following the presentation, there was a 10-minute Q & A session for Dr. Denner.

The Committee Discussion resumed with Questions for Session 1, the following discussion question was presented to the Committee:

Discussion Question #2:

2. Archiving of source animal, product, and patient samples for up to 50 years is the current FDA expectation outlined in FDA-issued guidance titled, "Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans" (December 2016). Archived samples can aid in investigation of adverse events, and the archiving recommendations apply to xenotransplantation products, including those that have had ex vivo contact with animal cells, but are not themselves of animal origin. Please discuss whether the expectations for archiving of patient samples should be modified in terms of length of storage and/or sample sizes.

a. Please discuss technologies that could be used to analyze cell banks and final products and that might be sufficiently sensitive to allow for modification of archiving requirements.

b. Please discuss conditions that would alter the expectations for patient follow-up.

c. Please discuss conditions, if any, under which patient follow-up for disease transmission should not be required.

d. Please discuss conditions under which recipients of xenotransplantation products should be allowed to donate blood or tissues/organs.

Summary of Discussion:
The committee agreed that DNA, RNA, PCR testing and serological testing are suitable technologies, and that next-gen sequencing is more sensitive but expensive and limited by informatics. The committee agreed that the 50-year requirement for archiving seems unreasonable and could be modified for some types of xeno products.

The committee discussed conditions that would alter the expectations for patient follow-up depending on the detection of illness, known pathogens, and newly identified pathogens.

The committee did not identify conditions under which patient follow-up would not be required because of the number of unknowns.

The committee agreed that there are too many unknowns regarding infectious disease transmission and novel pathogens to comment on recipient donation of blood or tissues/organs.

The committee agreed that different standards might be applied to different types of xeno products and recommend the FDA consider modification of the current guidelines to address the potential risk based on product type. The committee agreed that it would be reasonable to

lower the requirements for archiving and sampling when human cells are exposed to well-characterized xeno cell lines.

After the Committee Discussion of Questions for Session 1 concluded, the Committee had a 20-minute break and then moved to Session #2: Animal Organs and Cells for Transplantation into Human Subjects and Their Associated Risks.

For the start of Session 2, the FDA Speaker, Dr. Deborah Hursh, gave a presentation on "Considerations for the Characterization of Xenotransplantation Products as Biologics Question 3." Immediately following the presentation, there was a 10-minute Q & A session for Dr. Hursh.

During the Committee Discussion of Questions for Session 2, the following discussion questions were presented to the Committee:

Discussion Question #3:

3. Pig cells or organs transplanted into humans are FDA-regulated articles and are subject to regulatory requirements such as identity, purity, and potency. Please discuss assays or testing strategies that might be appropriate to perform prior to transplantation to evaluate the safety and efficacy of these articles.

Summary of Discussion: *The committee supported requirements for safety testing, including sterility, mycoplasma, and endotoxin testing, with herd management playing a role in limiting the microbial contamination. The committee supported testing for the presence of desired genetic modifications as a necessary component of product characterization. In-vivo testing of the donor animal to determine purity and identity whether through biopsy of organ, testing of adjacent tissues, or functional testing of the organ in the donor animal is needed. The committee discussed assessment of the donor organ pre-harvest to show that it is suitable for replacement therapy.*

The committee suggested that an internationally harmonized approach for the safety of xenotransplantation products should be considered.

Dr. Lisa Butterfield handed the meeting over to the DFO who adjourned the meeting on June 29, 2022, at 4:21 PM EDT.

On Day 2, June 30, Dr. Lisa Butterfield, the Chair, called the meeting to order. The DFO, Ms. Christina Vert, made administrative remarks, conducted roll call and invited the

committee members to introduce themselves, and read the Conflict of Interest (COI) statement into the public record. There were no conflict-of-interest waivers issued under 18 U.S. Code Section 208 in connection with this meeting. During the open session, CTGTAC members, consultants, FDA speakers, Guest Speakers, staff, and the public speakers all participated via the Adobe Connect web conference.

The meeting continued with Session 2: Animal Organs and Cells for Transplantation into Human Subjects and Their Associated Risks. The Guest Speaker, Dr. Richard Pierson, gave a presentation on "Xenotransplantation: Immunosuppression and Prospects for Tolerance". Immediately following the presentation, there was a 10-minute Q & A session for Dr. Pierson. This was followed by another Guest Speaker, Dr. Eckard Wolf, who gave a presentation on "Source Animals with Intentional Genomic Modifications." Immediately following the presentation, there was a 10-minute Q & A session for Dr. Wolf.

During the Committee Discussion of Questions for Session 2, the following discussion questions were presented to the Committee:

Discussion Question #4:

4. Transplantation of animal cells and organs into humans is associated with hyperacute rejection, vascular injury, cell-mediated rejection, and chronic rejection. Options for controlling rejection include genetic modification of donor pigs and modulation of the immune response in the recipient. Please discuss the most promising strategies to prevent rejection of pig organs. In your discussion, please consider the balance between the potential benefits of the desired genetic modifications and/or immune response modulation and the potential for detrimental transplant outcomes.

Summary of Discussion: *The committee agreed that genetic modifications to animal cells and organs should be optimized to decrease the risk of rejection in the recipient. The committee discussed the utility and limitations of preclinical studies using pig-to-non-human primate (NHP) transplant models and noted that some genetic modifications may need to be different based on species requirements.*

Following the Committee Discussion of Questions, the committee had a 34-minute lunch break. Once completed, a 15-minute Open Public Hearing (OPH) session was held from 1:00 p.m. to 1:18 p.m. in which one pre-registered public speaker made a presentation and another gave an oral statement. The names of the OPH speakers and their remarks may be obtained from the transcript posted on the website. Following the OPH session, there was a Committee Discussion of Questions session with Committee Members and Temporary Voting Members.

For the continuation of Session 2: Animal Organs and Cells for Transplantation into Human Subjects and Their Associated Risks, the FDA Speaker, Dr. Patricia Beaston, gave a presentation on "Clinical Considerations for Functional Studies of Pig Organs." Immediately following the presentation, there was a 10-minute Q & A session for Dr. Beaston. This was followed by a Guest Speaker, Dr. Kristi Helke, who gave a presentation on "Pigs in Toxicology: Differences in Metabolism and Background Finding May be Breed Dependent". Immediately following the presentation, there was a 10-minute Q & A session for Dr. Wolf followed by a 10-minute break.

During the Committee Discussion of Questions for Session 2, the following discussion questions were presented to the Committee:

Discussion Question #5:

5. Transplantation of pig cells and organs is intended to provide replacement for non-functioning/damaged human cells and organs. Therefore, it is important to understand the characteristics of these cells or organs in the pig to ensure they have the characteristics needed to provide replacement therapy for the human recipient before transplantation. And it is important to monitor these cells and organs to demonstrate that they provide the expected functions after transplantation. Please discuss existing data to address the following issues related to pig cells and organs intended for transplantation into humans:

a. The ability of the target pig organ to support full organ function in humans.

b. The natural aging of the target organ in the pig relevant to expected organ function over time in humans.

Summary of Discussion: *The committee agreed that there are insufficient data on homology between pig renal physiology and human renal physiology. The transplanted xeno organs harvested from young pigs may continue to grow to the adult size of the donor animal species. The committee discussed current challenges in identifying the risks of a physiologic mismatch.*

Discussion Question #6:

6. Transplanted pig organs are likely to be exposed to a variety of drugs that were not routinely used in the donor animals. Such drugs could include products to treat the recipient's underlying medical condition(s) (e.g., diabetes, hypertension), as well as drugs (e.g., immunosuppressants) intended to ensure the success of the transplant. The transplanted organ may alter the pharmacodynamic and pharmacokinetic profiles of these drugs, with consequences for the medical management of the recipient. In addition, these

drugs could be toxic to the transplanted organ. Please discuss the importance, limitations, and feasibility of studies of such drugs in the pig model prior to transplanting the pig organ into humans.

Summary of Discussion: *The committee agreed that additional data are needed. The value of including older pigs that may have conditions/diseases similar to that of target human recipients was also discussed. Pig studies should assess drug metabolism, as well as hormone-receptor interactions between pig organs and human cells and tissues. The evaluation of immune suppressants that will be administered to the human recipients was discussed, including that in-vitro studies may be used to answer some questions regarding immune suppressants. The committee suggested that some of the questions regarding drug compatibility may be completely investigated only in the clinical studies.*

After the Committee Discussion of Questions, Dr. Peter Marks, Director of the Center for Biologics Evaluation and Research, provided closing remarks.

Dr. Lisa Butterfield handed the meeting over to the DFO who adjourned the meeting on June 30, 2022, at 3:43 PM EDT.

Additional information and details may be obtained from the transcript and the recording of the webcast of the meeting may be viewed at:
https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisory-committee-june-29-30-2022-meeting-announcement-06292022

Direct Link to Recording of the Open Session:

- Day 1 June 29 link: https://youtu.be/DobR-4h8YA0
- Day 2 June 30 link: https://youtu.be/r8ea5NjLEW0