UNOS℠

Department of Health and Human Services (HHS), Food and Drug Administration (FDA)

2025-07568 Public Health Service Guideline (PHS) on Infectious Disease Issues in Xenotransplantation

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Cover Letter

VIA ELECTRONIC FILING – https://www.regulations.gov/

June 26, 2025

The Honorable Martin A. Makary M.D., M.P.H.
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

RE: Proposed Collection; Comment Request; Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation

Dear Commissioner Makary:

The United Network for Organ Sharing (UNOS) appreciates the opportunity to comment on the "Proposed Collection; Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation," published in the Federal Register on May 1, 2025. UNOS is a leader in developing and advocating for innovative solutions to strengthen the national donation and transplantation system and save more lives.

UNOS is a mission-driven non-profit based in Richmond, Virginia. As UNOS, we develop innovative technologies and initiatives, conduct data-driven research and analysis, provide expert consulting services, and advocate for patients. For more than forty years, we have helped operate the nation's Organ Procurement and Transplantation Network (OPTN) under contract with the U.S Government. As an OPTN contractor, we leverage data and advances in science and technology to continuously strengthen the system, increase the number of organs recovered and the number of transplants performed, and ensure patients across the nation have fair access to a transplant.

Xenotransplantation represents not only a breakthrough in medical science but also a vital source of hope for the more than 100,000 individuals currently awaiting lifesaving organ transplants. At UNOS, our researchers have partnered with healthcare industry experts to conduct research into the impact xenotransplant therapy could have on patients and medical decisions. It is the right time to understand the public's perception of xenotransplant, so any concerns will be addressed appropriately to enable the adoption of xenotransplantation.

Our team's data-driven approach to improving patient care and research addresses critical questions, such as public acceptance of porcine transplants and healthcare providers' concerns regarding their implementation. UNOS' team leverages our in-house expertise across a wide range of disciplines, including genetics, biology, public health, ethics, biomedical engineering, artificial intelligence, computer science, and biostatistics to foster a collaborative environment to promote innovation.

UNOS has been a cornerstone in standardizing, collecting, and distributing data for organ donation and transplantation, playing a vital role in supporting the national transplant system and informing regulatory decision-making. Our expertise spans the management of large, complex datasets, the development and refinement of national transplant policies, and the use of advanced data visualization tools to make critical information accessible to stakeholders. Through a robust data collection and documentation system powered by ServiceNow, we ensure accurate tracking, reporting, and continuous

improvement. Our collaborative approach brings together insights from medical, scientific, and community stakeholders.

Responses to Questions

Question 1: Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility

UNOS strongly supports the FDA's initiative to gather detailed data on xenotransplantation clinical trials and procedures. Patient safety is paramount due to the uncertain long-term risks associated with xenogeneic infections and the possibility of pathogens emerging long after transplantation. UNOS agrees with the FDA's requirement to keep records for 50 years and to implement comprehensive monitoring protocols, which is both prudent and essential.

Equally important is public health protection. The proposed cross-referencing system, which links transplant recipients, the xenotransplantation products they receive, the source animals, and the facilities involved will help to enable a swift and effective response should any infectious disease concerns arise. In addition to data collection related to infectious disease monitoring, UNOS recommends creating a set of Good Manufacturing Practices (GMP) standards for organs developed for xenotransplantation, similar to the GMP standards that exist for medicinal products to ensure they are consistently produced and controlled to the quality standards appropriate for their use.

Xenografts for humans are complex to make, and it is difficult to "test" xenografts prior to transplant into a human patient. Quality issues during manufacturing of a xenograft may not surface until years after transplantation. A xenotransplant Good Manufacturing Process (xtGMP) would reduce risk to recipient patients and the public by helping enforce quality standards at manufacturing facilities. Data captured for this purpose can be used for monitoring and auditing.

Finally, the initiative supports scientific advancement. By standardizing data collection across trials and procedures, researchers will be better equipped to study and understand the safety and efficacy of xenotransplantation, ultimately driving progress in this promising field.

Question 2: The accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used

Based on UNOS's experience implementing similar systems, there is a greater burden than the FDA's current estimate of 62.12 hours per year to reduce the overall reporting burden and to implement the new data collection system.

The initial development of cross-referenced record systems often requires more time than projected, as designing, validating, and testing such databases can be a complex process, especially when integrating with existing clinical systems. The estimate should include the time and resources needed for comprehensive staff training on new data collection protocols, standardized terminology, specimen handling, cross-referencing methods, privacy and security requirements, and quality assurance procedures.

Long-term maintenance of these records, particularly over a 50-year period, also presents significant challenges. This includes not only the storage of complex, linked records such as imaging and genomic data, but also the need for periodic technology migration, ongoing security updates, maintaining accessibility, and ensuring robust backup and disaster recovery systems. We recommend the FDA include additional time and resources to build a robust system that standardizes data collection, maintains controls, and allows for integration with existing clinical databases.

Question 3: Ways to enhance the quality, utility, and clarity of the information to be collected; and to improve the quality and utility of collected information

UNOS recommends a focus on standardization by developing standardized data collection forms and terminology to ensure consistency across all reporting entities. This includes creating a unified data dictionary with comprehensive definitions for all data elements, like OPTN's Standard Transplant Analysis and Research (STAR) files. We also advise the adoption of standardized taxonomies, such as existing medical coding systems like ICD-10 and the development of xenotransplantation-specific codes where needed. Establishing common data elements (CDEs) for xenotransplantation research will facilitate data pooling and meta-analyses.

UNOS further recommends close coordination between FDA xenotransplantation oversight and OPTN systems, leveraging their experience managing complex transplant data. This coordination should include the development of shared patient identifiers to link xenotransplant recipients who may later require human organ transplants, and adverse event reporting coordination through the creation of a shared taxonomy for adverse events and implementing automated notifications for critical safety events. The FDA should prioritize patient tracking and registry integration by linking longitudinal xenotransplant history with standard transplant recipient records and enabling a secure linkage between OPTN research databases and xenotransplantation registries.

Establishing a collaborative and standardized registry in the United States is essential. Key barriers to developing such a registry include securing adequate resources for both the private sector and government. As xenotransplantation is an emerging field, new data standards will need to be created, thus offering the U.S. Government a unique opportunity to become the international leader in xenotransplantation. By defining the standards in the field, the U.S. Government can establish best practices that follow the model of existing data standards to ensure interoperability and effective linkage with OPTN data.

Presently, there is no required, standardized, and centralized database for donor or patient data related to xenotransplantation, which represents a significant gap and hinders research into patient outcomes, policy development, and best practices. While a voluntary international inventory exists, it does not collect sufficient data for robust research. It is important to note that the current international registry for xenotransplantation captures only the occurrence of procedures and limited basic information (e.g. type of source animal; the organ involved). It does not collect detailed clinical data; as a result, the scope of research that can be conducted using this registry is extremely limited. It cannot support meaningful analysis of patient outcomes, the development of best practices, or the assessment of xenotransplant safety. In contrast, we specifically designed UNOS' proposed data collection tool to enable these critical areas of research.

To supplement the data standardization and ingestion paradigm outlined above, UNOS can employ an array of artificial intelligence (AI) methods to (1) aid in standardization and (2) improve data quality through automated measures. Natural language processing (NLP) can systematically extract structured information from unstructured clinical notes or survey responses, converting narrative text into standardized, searchable data elements. Machine learning (ML) models can continuously monitor data for inconsistencies and errors, flagging issues in real-time to ensure dataset integrity. Advanced clustering and anomaly detection algorithms can identify novel safety signals and outcome patterns that traditional methods might miss, while predictive modeling can enhance risk stratification and enable dynamic monitoring adjustments.

Question 4: Ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology

UNOS commends the FDA for its thoughtful approach to xenotransplantation oversight and supports the proposed information collection activities. UNOS encourages the FDA to standardize data collection and shift from voluntary to required data collection instruments. Comprehensive monitoring and record-keeping requirements are essential for ensuring patient safety and public health protection as this promising technology advances. With careful implementation and ongoing refinement, this information collection system will provide the foundation for safe and effective xenotransplantation while minimizing the burden on the transplant community.

The requirement for a cross-referenced record system is essential for epidemiological investigation. Technical specifications should include globally unique identifiers for all entities, hierarchical structures for intuitive organization, and master cross-reference tables. We recommend specifying required terminologies (SNOMED CT, LOINC, RxNorm) and incorporating interoperability standards (FHIR) during design to support data consistency and streamline its collection.

For healthcare worker monitoring, the FDA should incorporate lessons from HIV and hepatitis programs, including comprehensive baseline and follow-up testing, risk stratification based on exposure, and personalized monitoring. Data integration with public health reporting pathways is also important, and we recommend the FDA specify which of these pathways should be integrated.

Shared infrastructure and resources are also essential; a consortium approach can help share data management costs, while cloud-based solutions and academic partnerships can reduce the IT burden for smaller facilities. Streamlined reporting mechanisms—such as exception-based reporting and automated report generation—can further reduce administrative workload. As part of our forward-looking vision, we recommend maintaining certain specimens and records for 50 years following xenotransplantation, supported by a record system that enables seamless, accurate, and rapid linkage between specimen archives, recipient medical records, and source animal data.

In our article "UNOS' high expectations for IT security standards – and what's next[1]," we provide an overview of how UNOS approaches system enhancements through cybersecurity best practices. Our Organ Center receives an average of 170,000 organ offer notifications each month, and our teams work diligently to protect patient and system data 24/7/365 by adhering to Federal cybersecurity standards and regular system enhancements that strengthen and reinforce the system. We are eager to contribute our expertise to the FDA to ensure everyone can live without limits.

Regarding the record retention period, the 50-year requirement is appropriate because of the potential for long-latency infections. UNOS recommends standardizing data formats (such as XML or JSON), establishing a migration schedule for data format updates every 10 years, specifying minimum cloud storage standards (including geographic redundancy and encryption), and maintaining comprehensive metadata. Data security should evolve with current encryption standards (like AES-256), role-based access control, and robust de-identification protocols.

Data submission should be automated through FHIR APIs to minimize burden to both clinical and IT staff. The use of terminology and interoperability standards will substantially reduce the need to surface, translate, and transform relevant data for submission. This reduces up-front system integration

[1] United Network for Organ Sharing (UNOS), "UNOS' High Expectations for IT Security Standards – and What's Next," UNOS, February 20, 2025, https://unos.org/news/unos-high-expectations-for-it-security-standards-and-whats-next/.

complexity and streamlines future changes to data collection as xenotransplantation evolves. Narrow-task focused AI can supplement discrete data collection to extract relevant information directly from PDFs and clinical documentation, significantly reducing manual data entry requirements. Workflow automation can streamline pipelines through robotic process automation, integrations with EHR systems, and smart scheduling algorithms that minimize clinical workflow disruption.

We have extensive experience in leveraging advanced data management, analytics, and quality assurance strategies to support regulatory decision-making and oversight in complex healthcare environments. We recommend implementing risk-based monitoring strategies, such as adaptive monitoring that intensifies based on safety signals or patient risk factors, and trigger-based reporting that establishes specific clinical triggers to start enhanced monitoring protocols. Stratified surveillance can vary monitoring intensity based on factors like source animal species, recipient immune status, and healthcare facility capabilities.

Conclusion

Positioned at the forefront of innovation, UNOS is committed to building and integrating solutions that enhance patient safety monitoring, guide policy evolution, and drive growth in the field both nationally and globally. We welcome the opportunity to partner with the FDA as a proven leader in organ transplantation through our work operating the OPTN. We offer our expertise, resources, and capabilities to help advance the Agency's xenotransplantation endeavors to promote patient safety through infectious disease control and prevention measures.

We can support xenotransplantation projects from inception to production by partnering with FDA to build a coordinated, interoperable, and forward-compatible information infrastructure. Our collective efforts will allow xenotransplantation to evolve responsibly and transparently.

Using emerging Agentic AI systems, the FDA can enable autonomous workflow development and management, where AI agents can dynamically combine multiple building blocks - from predictive modeling to document parsing - as integrated tools to address complex data challenges with minimal human intervention. These agents will act semi-autonomously to implement and refine data collection and analysis workflows, and perhaps, in the near future, design workflows to adapt in real-time to changing requirements and study needs.

With careful implementation and ongoing refinement, this information collection system will provide the foundation for safe and effective xenotransplantation while minimizing the burden on the transplant community. UNOS encourages continued dialogue between FDA, OPTN, as well as commercial and academic researchers, and clinical practitioners to align regulatory requirements with real-world implementation capacity. As the field advances, a shared commitment to rigorous oversight, scientific integrity, and practical feasibility will be essential to realize the full promise of xenotransplantation while safeguarding public trust.

Sincerely,

Andrew Klein, M.D., MBA
Chief Medical Officer, UNOS