Regulatory Considerations and Oversight: A US Perspective

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Judith A. Arcidiacono, Evgenij A. Evdokimov, and Harlan J. Howard

Introduction

Xenotransplantation has been proposed to alleviate the shortage of organs, tissues, and cells available for human transplantation since the 1990s. Early strategies focused on cellular products such as porcine-sourced pancreatic islets and liver assist devices seeded with porcine-sourced hepatocytes. Today, first-in-human (FIH) clinical trials are focused on whole organ xenotransplantation (heart, kidney, and lung). This is due to increased understanding of the mechanisms of xeno-rejection and molecular tools available for the intentional genomic alteration of source/donor animals to prevent rejection.

Despite the potential benefits of xenotransplantation, some challenges remain. Risks associated with the use of xenotransplantation products include the transmission of known and unknown pathogens to the patient, the patient's personal contacts, health care professionals, and the general population. Rejection of source/donor animal cells, tissues, or organs can cause adverse reactions in the patient. Patients receiving xenotransplantation products will likely need long-term immunosuppression, which entails risks that are currently unavoidable. Physiological and metabolic incompatibility between the source/donor animals and the recipient are additional risks associated with the use of xenotransplantation products.

J. A. Arcidiacono (✉)
OTP, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA
e-mail: Judith.Arcidiacono@fda.hhs.gov

E. A. Evdokimov · H. J. Howard
DABCT, ONADE, Center for Veterinary Medicine, Food and Drug Administration, Rockville, MD, USA
e-mail: Evgenij.Evdokimov@fda.hhs.gov; Harlan.Howard@fda.hhs.gov

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To overcome some of the immunological barriers to xenotransplantation, animals with intentional genomic alterations (IGAs) have been developed and the animals' organs have been used in preclinical studies [1]. The alterations include removal of pig antigens, addition of human genes that are naturally absent in the pig, or substitution of pig antigens with human counterparts. Potential adverse effects of IGAs in animals include altered organ function, metabolic changes, and other factors that may affect suitability of organs for xenotransplantation. Preclinical animal models for xenotransplantation may help evaluate these possibilities.

History of Xenotransplantation Regulation

In the early 1980s, virologists came to understand that the Human Immunodeficiency Virus (HIV) originated from a genetic shift in the Simian Immunodeficiency Virus (SIV) that allowed it to become zoonotic, transmissible from primates in Africa to humans [2]. This realization prompted immediate alarm over the risk of zoonoses arising from exposure to unknown or unidentified animal viruses as the result of a xenotransplantation. To address this concern, the US Secretary of the Department of Health and Human Services (DHHS), with experts from the Center for Disease Control and Prevention (CDC), FDA, the National Institutes of Health (NIH), and the US Public Health Service (US PHS) convened workshops and advisory committee meetings with infectious disease experts, veterinarians, transplant surgeons, and international regulators to develop US policy for xenotransplantation. These discussions resulted in the publication of guidance for the development and use of xenotransplantation products: *Public Health Issues Posed by the use of Non-Human Primate Xenografts in Humans* (1999);[1] *Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation* (2001) [3]; *Guidance for Industry: Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans* (2003, revised 2016) [4]. Today, FDA continues to take part in the development of national and international policy on regulatory requirements for xenotransplantation products with the World Health Organization (WHO) and the International Xenotransplantation Association (IXA) [5].

FDA Definition of Xenotransplantation

FDA defines xenotransplantation as "any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source; or (b) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or

[1] Public Health Issues Posed by the use of Non-Human Primate Xenografts in Humans (1999), this document is no longer available. See Federal Register notice at https://www.federalregister.gov/documents/1999/04/06/99-8439/guidance-for-industry-public-health-issues-posed-by-the-use-of-nonhuman-primate-xenografts-in-humans.

organs" [4]. These products are regulated as biologics under section 351 of the Public Health Service (PHS) Act (21 U.S.C. 321 *et seq*.). Examples of xenotransplantation products include viable porcine hearts with the vasculature, porcine-derived pancreatic islets, and viable porcine skin.

Xenografts are defined by FDA as acellular (decellularized) products derived from animal tissues that are devoid of viable and non-viable cellular material regardless of the method used for decellularization [4]. Examples of these products include decellularized prosthetic heart valves derived from bovine or porcine tissues. Xenografts may be regulated as Class II or Class III medical devices by the FDA requiring premarket clearance (510(k) premarket notification) or premarket approval (PMA) [6].

Current Paradigm for Regulating Xenotransplantation Products in the United States

FDA has a well-established paradigm for the regulation of xenotransplantation products, including the regulation of IGAs in animals [7]. Tissues or organs from animals with IGA(s) may be intended for use as xenotransplantation products in humans. In this circumstance, there are two products, the IGA and the human xenotransplantation product, that two different FDA centers regulate: the Center for Veterinary Medicine (CVM) and the Center for Biologics Evaluation and Research (CBER).

CVM evaluates IGAs in animals that serve as sources of products for xenotransplantation, whereas CBER evaluates the xenotransplantation products derived from animals with IGAs that are used in human patients. CVM approval of IGAs in animals does not authorize the use of the xenotransplantation products derived from these animals in humans. Rather, the use of these products in human patients must go through a rigorous pre-clinical and clinical evaluation prior to CBER's approval of a biologics license application (BLA). Each Center's evaluation processes are complementary and can be carried out in parallel while sponsors are collecting safety and effectiveness data to support each Center's approval requirements. In the end, CVM's approval of the IGA necessarily precedes CBER's BLA approval(s).

During evaluation, the two Centers make independent regulatory and scientific determinations that follow each Center's existing policies and authorities. FDA reviewers from both Centers work together to ensure a comprehensive and non-redundant evaluation of xenotransplantation source animals and products [8]. CBER evaluates many aspects of manufacturing and product quality for xenotransplantation products prior to clinical trials and continues with more detailed assessments as product development proceeds as part of the investigational and approval process. These steps involve evaluation of animal husbandry, animal health, and manufacturing, clinical, preclinical, and statistical information supporting licensing of the proposed xenotransplantation product. CVM's evaluation focuses on the characterization, durability, and safety and effectiveness of the IGA(s) in animals that will be used as a source of organs and tissues for xenotransplantation.

The general principles that FDA considers as it reviews xenotransplantation products are described below. This is not an exhaustive list, but it provides a better understanding of how FDA regulates xenotransplantation products and ensures their safety and effectiveness.

CVM Oversight of Intentional Genomic Alteration(s) in Animals

CVM regulates IGAs in animals under the Federal Food Drug and Cosmetic Act (FD&C Act) (21 U.S.C 321 et seq.) and its implementing regulations (21 Code of Federal Regulations (CFR) Part 511 & 514). In 2009, CVM issued Guidance for Industry 187, which clarified how FDA's statutory and regulatory requirements apply to the regulation of IGAs in animals, including those intended for use in xenotransplantation. This guidance document explains the regulatory process for IGAs in animals, including approvals, provides recommendations to sponsors of IGAs in animals on how they can address FDA regulations, and aligns each step of the review process with these regulations. In 2017, CVM released a draft of the revised guidance that clarified that the scope of the guidance includes IGAs developed using genome editing technology [7]. Of note, some sponsors of IGAs in animals for use as sources of cells, tissues, or organs for xenotransplantation may choose to introduce single or multiple heritable IGAs into an animal lineage, i.e., disruption or knock-out of endogenous porcine genes and insertion of human gene sequences in the pigs' genome, with the aim of making biological materials from these pigs more immunologically compatible with the human immune system. CVM would generally consider a line of pigs with multiple IGAs to be subject to a single regulatory determination/approval in which all IGAs are considered as part of the safety and effectiveness assessment.

As applicable to CVM's oversight of IGAs in animals, to address the requirements related to safety and effectiveness of quality manufactured products, the risk-based review covers the following general areas: (1) product characterization (molecular characterization of the IGA and molecular characterization of the lineage), (2) phenotypic characterization of animals' IGAs (characterization of the phenotype and evaluation of the impact of the IGA on the health of the animals); (3) durability assessment and plan (demonstration that the IGA is durable (consistency of genotype/phenotype) over time/multiple generations and continued monitoring post-approval with corresponding reports submitted to CVM), (4) food safety (with recognition that source animals do not enter the human or animal food supply without prior authorization), (5) environmental impact, and (6) effectiveness. This review process constitutes a life-cycle regulatory approach where CVM evaluates data and information collected prior to approval and continues monitoring the safety and effectiveness of these products after approval until they are discontinued and/or removed from the market. The steps of the review process are described in the draft Guidance for Industry 187 [7] and summarized below.

Product Characterization

CVM's review process focuses on hazard identification and hazard characterization. Product Characterization, as described here, includes the Product Identification, Molecular Characterization of the IGA, and Molecular Characterization of the Lineage steps of the review process. Product Identification describes the IGA(s), the lineage of animals containing IGA(s), and the purpose of the IGA(s) (i.e., their intended use in the animals). Molecular characterization steps focus on assessing the design and ultimate incorporation of the IGA(s) in the animal's genome, incorporating concepts related to chemistry, manufacture, and controls in the early stages of development. Data collected during product characterization, in general, provide a foundation for future development of methods and assays that aim to ensure the safety and effectiveness of the IGA(s). Characterization should encompass a full description of the proposed IGA(s), the intended function, and how the IGA(s) was (were) achieved, supported by data that fully characterize the proposed IGA(s) in the animal's genome, including location and stability. Careful attention should be given to effects associated with the proposed IGA(s). Such effects can be intended or unintended, depending on the location of IGAs in the animals' genome and the function of the altered gene. The intended effects are associated with IGA(s) successfully targeting the intended locus in the genome. Unintended effects include off-target alterations or unexpected alterations at the target site (e.g., insertion of unintended sequences at the target site). These effects and risks associated with identified hazards are considered further under the Phenotypic Characterization, Food Safety, and Environmental Impact steps of the review process. CVM's conclusions about data and information reviewed under the Product Characterization step may also help to inform CBER's risk/safety assessment, which focuses on the use of products derived from animals with IGAs in human patients. Robust molecular characterization of the IGAs in the animals is necessary prior to proceeding with human trials.

Phenotypic Characterization

Demonstrating the health and well-being of animals with IGA(s) serving as sources of cells, tissues, or organs used in xenotransplantation is critically important for both CVM's and CBER's review processes. CVM's evaluation focuses primarily on overall herd health management and potential risks associated with the introduction of IGAs into the genome of the animals. CBER, while also considering many of these questions, has an additional consideration for health assessments on individual candidate animals used as sources of xenotransplantation materials.

Examples of the types of animal health and safety data evaluated in support of CVM's approval can be found in the Freedom of Information Summary for a December 2020 approval of an IGA in domestic pigs that may serve as sources of food or human therapeutics, including xenotransplantation.[2] CVM has also approved

[2] https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/10168.

other "biopharm" products from animals with IGAs. Although these products are not intended for the production of cells, tissues, and organs for xenotransplantation, the data and information sponsors used to support animal safety could also apply to xenotransplantation products. Examples of these approvals include IGAs in chickens,[3] rabbits,[4] and goats.[5] For these approvals, sponsors included and CVM reviewed factors such as: (1) general management/husbandry procedures, including housing, nutrition, reproduction, health assessments (e.g., routine periodic and scheduled veterinary examinations), and procedures (e.g., vaccinations, other preventative health measures); (2) physical and biological containment/security, to assure the health of the animals as well as a full accounting of the animals and any biological materials collected from them; (3) other considerations based on the product's particular risk profile, such as growth of animals with IGAs and/or their organs, and (4) euthanasia of source animals according to guidelines of the American Veterinary Medical Association [9]. Sponsors may conduct studies to demonstrate animal safety as necessary to assess the risk profile of the IGA in the animal.

By reviewing data collected on the animals, CVM verifies that sponsors are implementing and following their documented procedures. Such review occurs on data formally submitted to CVM and/or during FDA inspections of sponsors' facilities.

Inspections may occur at any time during the lifecycle of product development, and generally occur prior to the approval of the application. Periodically after approval, FDA performs surveillance inspections to assure that the product remains consistent with the findings during pre-approval development.

The sponsor's scope of data collection is dependent on the level and nature of risks to the animal associated with the introduction of the IGAs into the animals. Like product characterization described above, CVM's evaluation of animal safety helps lay the groundwork, not only for hazard identification and risk assessment for other parts of CVM's review processes, but also for CBER's risk/safety assessments targeting the downstream xenotransplantation product. The complexity of functions of the cells, tissues, or organs that would occur in humans may influence the depth of evaluation sponsors may need to conduct to support development of the final human product.

Durability Assessment and Plan

One aspect of producing a quality product is ensuring the stability and consistency of IGA(s) in animals both pre- and post-approval. CVM's evaluation of stability and consistency of the IGA(s) in animals is supported by review of genotypic and phenotypic data demonstrating durability of the genetic modification(s) (known as the

[3] https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/2558.

[4] https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/6927.

[5] https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/859.

durability assessment) as well as data to support continued durability, safety, and effectiveness post-approval (known as the durability plan).

The durability assessment entails an evaluation of the genotypic and phenotypic stability over time (e.g., over multiple generations or cohorts of the animals). This evaluation builds on data collected and evaluated during product characterization and additional molecular characterization, phenotypic characterization, and effectiveness data that sponsors may have collected during the development process. These data and information serve as a basis for the development of validated methods and assays for monitoring the stability of IGAs in animals' genomes and traits associated with these IGAs as part of the durability plan (e.g., sequence-based assay(s) demonstrating the intended genotype, and protein expression assay(s) confirming a gene knock in/out).

The durability plan is a commitment by sponsors of IGAs to assess their product (i.e., IGA(s) in animals with any associated traits) to demonstrate that the IGA(s) continue to be safe and effective post-approval. In addition to providing data to support durability of the IGA(s) post-approval, there are also requirements for post-approval reporting as described in 21 CFR 514.80. Post-approval reporting and monitoring support the continued health and well-being of the animals with IGA(s).

Although the focus of the plan is on the durability, safety, and effectiveness of the IGA(s), it closely aligns with the safety and quality assurance procedures considered by CBER for the xenotransplantation product. CVM and CBER's oversight are complementary and comprehensive for these products. For example, CVM monitors for diseases in animals with IGA(s) that may also be important considerations for CBER's evaluation of adventitious agents in tissues or organs for transplantation in pre-clinical and human clinical studies.

Food Safety

Although animals with IGAs intended for use in xenotransplantation are not likely to be used as sources of human or animal food, food safety is assessed if the source animals are from a recognized food animal species (e.g., swine). In the reviews of IGAs in animals of food-producing species that will be used for biomedical and not food use, CVM has focused on ensuring that there are adequate controls in place to prevent animals from inadvertently entering the food supply. CVM considers the level of concern for humans consuming edible products, and ensures that validated, suitable detection methods are in place that can distinguish the animals from those without IGA(s) in the unlikely event an animal with IGAs inadvertently entered the food supply.

If a sponsor intends to introduce their animals with IGA(s) into the food supply, CVM conducts a rigorous evaluation to determine whether edible tissues derived from the animal are safe for humans and animals consuming them [7].

Environmental Impact

In accordance with the National Environmental Policy Act (NEPA), the Agency evaluates the potential for significant environmental impacts from approving an application for an IGA in an animal, including the development and commercialization of animals with IGA(s). Under NEPA, FDA must determine if major Agency actions will have a significant impact on the environment. The approval of an application (21 CFR 514.1(b)(14)) is a major Agency action and evaluated by CVM as described in the draft revised Guidance for Industry 187 [7].

Effectiveness

CVM's evaluation of effectiveness focuses on the sponsor's claim(s) associated with IGA(s) in the animals. CVM focuses on the intended function of the IGA(s) in animals (such as the presence or absence of a protein introduced or knocked out by the introduction of the IGA(s)). CBER also considers the molecular aspects of IGA(s) and associated phenotypic traits in their review, however, they evaluate these aspects to determine whether the IGA(s) are appropriate for the successful function of xenotransplantation products in human patients in a clinical setting as part of CBER's effectiveness evaluation.

CBER Oversight of Human Biological Products

Xenotransplantation products are regulated as biological products under the authority of section 351 of the Public Health Service (PHS) Act (21 U.S.C. 321 *et seq*.) in CBER. If xenotransplantation products are to be used in a clinical investigation, an Investigational New Drug (IND) application must be in effect as specified by FDA regulations (21 U.S.C. 355(i); 42 U.S.C. 262(a)(3); 21 CFR 312). Introduction of a xenotransplantation product into interstate commerce requires an approved Biologics License Application (BLA) (21 CFR 601). To receive an approval, the clinical trial data submitted to FDA must demonstrate safety and effectiveness for its intended use.

CBER's assessments for xenotransplantation products include five major components: (1) source herd, (2) source animals from which the xenotransplantation product is derived, (3) product processing and testing (chemistry, manufacturing, controls), (4) preclinical assessments, and (5) clinical requirements.

Source Herd

FDA's regulatory approach for source animals used in xenotransplantation is focused on building layers of safety that include a balanced risk assessment and the use of best practices and validated technologies. The use of appropriate

source herds is the first line of defense against the risk of zoonoses. Specific recommendations for source herds can be found in the FDA Guidance for Industry: *Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans* [4]. Source herds should be bred from closed herds of known origin. These animals should breed two or more generations under specific-pathogen free (SPF) conditions prior to use for human transplantation products. Gamete donors should meet the same qualifications as donor animals. Sourcing of animal tissues or gametes from abattoirs is not acceptable.

Maintenance of animal herds used to derive xenotransplantation products should include screening and sentinel animal testing for infectious disease. The frequency, agents tested for, and the methods used for testing should be justified. Animal feed should be free of rendered animal material. Animal herds should be maintained in a well-controlled and monitored pathogen-free environment with appropriately trained staff. Plans for bio-secure transportation of the animal and/or the xenotransplantation product to the tissue harvest site and the clinical site should be in place.

Source Animals for Xenotransplantation Products

Source animals selected from a suitable herd from which the xenotransplantation product is derived should be placed in quarantine at least 3 weeks prior to harvest of the xenotransplantation product. The source animal should be assessed for general health and tested for infectious agents prior to entering quarantine and prior to harvesting of cells, tissues, or organs. Procedures should be in place to minimize infectious disease risks during harvesting and handling.

Animal Welfare

Source animal facilities and manufacturers of xenotransplantation products should have procedures in place for animal husbandry, tissue harvesting, and euthanasia of animals. Procedures should be approved by an appropriate Institutional Animal Care and Use Committee in accordance with the Animal Welfare Act (7 U.S.C. 2131, *et seq*.). In cases where funds are received from the PHS, procedures must also comply with the PHS Policy on Humane Care and Use of Laboratory Animals [10], according to Section 495 of the PHS Act (42 U.S.C. 289(d)), CBER recommends that source animal facilities be accredited by the AAALAC. Standards for accredited facilities when funds are received from the National Institutes of Health are provided in the National Research Council's Institute for Laboratory Animal Research, Guide for the Care and Use of Laboratory Animals [11]. Source animal facilities and production processes are subject to FDA inspection under Section 704 of the Act (21 U.S.C. 374) and Section 351(c) of the PHS Act (42 U.S.C. 262(c)) [4].

Chemistry, Manufacturing, and Controls (CMC): Product Processing and Testing

Manufacturers of xenotransplantation products are expected to follow current Good Manufacturing Practices (cGMP). The FDA uses a life-cycle approach for cGMP where manufacturers may implement manufacturing controls that are appropriate during Phase 1 of development and work towards full cGMP compliance as product knowledge and manufacturing experience advances (21 CFR 312.23(a)(7)). Given the public health risks of xenozoonoses, rigorous safety measures need to be in place at all stages of product development.

The regulatory requirements for biologics products outlined in 21 CFR 610 apply to xenotransplantation products. For example, 21 CFR 610.10 Potency, 21 CFR 610.12 Sterility, 21 CFR 610 13 purity, and 21 CFR 610.14 Identity require specific tests for each of these attributes on the final product or final container material, unless exempted from this requirement by the CBER Director. The strategies for meeting these standards depend on the type of product: cells, tissues, or organs. For example, sampling for testing of an organ used for xenotransplantation may include a whole organ biopsy. Surrogate samples from adjacent tissues may be used for identity, sterility, and viral testing. Tests for potency could be assays that measure the function of the organ prior to administration. For cells and tissues, testing can be done directly on the cells or tissues to be transplanted.

Preclinical Assessments

In general, preclinical evaluations provide rationale for a proposed therapy. Preclinical studies are designed to discern the mechanism(s) of action, identify safe starting dose levels and dose escalation schemes for a patient population, assess preliminary benefit/risk profiles, and identify parameters for clinical monitoring. Above all, these studies must provide sufficient information to evaluate whether “human subjects are or would be exposed to an unreasonable and significant risk of illness or injury” (21 CFR 312.42 (b)(1)(i)). Preclinical assessments of xenotransplantation products include appropriate consideration and/or analysis of risks from potential cross-species infections, immune reactions between source animal and recipient, and function of the xenotransplantation product. Proof of concept studies for xenotransplantation products should use animal models that resemble the disease being studied as closely as possible. In some situations, it may be advisable to use more than one species; in others, it may be possible to collect both safety and proof-of-concept data in a single study. Administration of the xenotransplantation product in a preclinical study should mimic the planned clinical transplantation procedure including the immunosuppression regimen, the use of an immune-isolation device, site and means of administration, and re-implantation of the product, if applicable. When animals with IGA(s) are planned for use, animals used for preclinical studies should have the same IGA(s) as the animal

intended to be used for human implantation. Such animals should be assessed by the CVM prior to the initiation of preclinical studies. FDA recommends that developers obtain feedback regarding design of preclinical studies via the INTERACT mechanism [12].

Clinical Requirements

Regulatory and scientific principles governing the conduct of clinical trials for xenotransplantation products, similar to those for other products, require the submission of an IND. Patient might qualify to access xenotransplantation products through FDA's expanded access/compassionate use pathway when no comparable or satisfactory alternative therapy options are available (21 CFR 312.300). Specific criteria must be met to qualify for expanded access [13]. Current Good Clinical Practice (GCP) guidelines are to be followed for all INDs.

A clinical trial may be initiated 30 days following receipt of an IND unless FDA imposes a Clinical Hold. The grounds for doing this are enumerated explicitly in regulation (21 CFR 312.42(b)). The most commonly cited are: "Human subjects are or would be exposed to unreasonable or significant risk of illness or injury" (21 CFR 312.42 (b)(1)(i)) and "The IND does not contain sufficient information required under 21 CFR 312.23 to evaluate the risks to subjects of the proposed trial" (21 CFR 312.42 (b)(1)(iv)). The factors to be weighed in deciding whether there is "unreasonable" risk include: the natural history of the indication selected for the investigation—with detailed description of inclusion/exclusion criteria—available alternative therapies, persuasiveness of the preclinical proof-of-concept data collected in studies using the same product as that to be investigated, the number and severity of safety signals observed during animal studies in the context of this indication, and the generalizable scientific data likely to be generated. Thus, a product intended to treat a serious or life-threatening condition (e.g., advanced invasive cancer, spinal cord injury) may have a different safety profile than would apply to a cosmetic indication.

As set forth in 21 CFR 312.22 (a), "although FDA's review of Phase 1 submissions will focus on the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the instigations will yield data capable of meeting statutory standards for marketing approval." For further details, see FDA Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products [14]. Common elements of early phase xenotransplantation clinical protocol, as for most products, include: a small number of subjects treated in a staggered pattern where the timing between treating the first and second subject and additional subjects will allow for a defined period of post-treatment monitoring for adverse events prior to treating the next subject, inclusion/exclusion criteria, a detailed safety monitoring plan that evaluates a range of clinical and pharmacodynamic endpoints to inform the design of later trials, monitoring for possible infections or signs of rejection, and informed consent, including risks to close contacts [5]. As for any human trial, sponsors of xenotransplantation clinical

trials are responsible for informing patients of new scientific information as soon as possible in the event that new information on risks benefits, or the need for additional treatment is needed [4]. Special considerations for xenotransplantation products include monitoring for potential zoonotic infections, adverse xenograft-related immune response(s), and physiological mismatch of the implanted/transplanted product in vivo.

Additional Considerations for Xenotransplantation Products

In addition to the points enumerated above, another special concern for xenotransplantation products is the potential for transmission of perhaps novel zoonotic diseases—particularly those that may have been difficult to detect by conventional culture methods—not only to subjects involved in trials but to the human population at large. Precautions to address this concern include logistics of donor material procurement, careful monitoring of subjects for immune phenomena that may be associated with rejection, appropriate salvage strategies should rejection occur, and collection of donor material and human subject material for detailed laboratory analyses.

It is crucial to coordinate procurement of the xenotransplantation source material, transportation from the animal facility to the harvesting/manufacturing site (if applicable), and then to the clinical site. The IND application should include a plan for biosecure transportation, which will be reviewed by CBER for acceptability.

To further evaluate risks of potential zoonoses, tissues and cells from source animals and human recipients should be collected and archived for future studies. The goals for establishing archives are to ensure the health and safety of recipients and their close contacts, and to provide a source of materials for "look back" in the case patient health issues or public health issues arise. Source animal samples should include portions of the harvested material (cells, tissues, or organ) and leukocytes from the source animal. These samples should be collected at the time of harvest, and at predetermined intervals. For human recipients, samples of blood, and plasma saliva, and leukocytes should be collected pre-transplant, post-transplant at pre-determined intervals, and post-mortem. Guidelines for sample archiving are outlined in the U.S. Public Health Service (PHS) Guideline on Xenotransplantation [3].

Concluding Remarks

When xenotransplantation was first introduced as a potential means to alleviate the shortage of human cells, tissues, and organs for transplantation, xenogeneic pancreatic islet and liver cells appeared to have the most potential. In the past several years however, the transplantation of xenogeneic organs has become closer to reality due to the availability of animals with intentional genomic alterations, pigs in particular.

Despite these advances, more studies are needed to ensure safe and effective xenotransplantation. FDA supports the responsible use of xenotransplantation products keeping in mind the welfare of animals and the health and safety human recipients and the community at large.

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