Regulatory Considerations and Oversight: A European Perspective

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Abbreviations

ATMP	Advanced therapy medicinal product
CAT	Committee for Advanced Therapies
CBMP	Cell-based medicinal products
CHMP	Committee for Medicinal Products for Human Use
DPF	Designated pathogen-free
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IXA	International Xenotransplantation Association
PERV	Porcine endogenous retrovirus
SACX	Secretary's Advisory Committee on Xenotransplantation
UKXIRA	United Kingdom Xenotransplantation Interim Regulatory Authority
WHO	World Health Organization

Introduction

Xenotransplantation into humans is defined as any procedure that involves the direct transplantation, implantation, or infusion into a human recipient of live cells, tissues, or organs from a non-human animal source, or indirect exposure, where human body fluids, cells, tissues, or organs that have had ex vivo contact with live non-human animal cells, tissues, or organs before being administered. This definition was posted on the website of the World Health Organization (WHO) but is no longer

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a search item on the WHO website. This aside, this definition is nowadays used worldwide, including regulatory agencies like the Food and Drug Administration (FDA) in the USA [1]. The European Medicines Agency (EMA) was from the beginning in 2000 more focused on xenogeneic cell-based therapy [2]. In Europe, also the European Parliament became recently interested in xenogeneic transplantation [3]. This chapter focuses on the first category mentioned above. Viable products for use in humans are called xenotransplantation products, to be differentiated from non-viable products that are called xenografts: this differentiation was first mentioned in regulatory documents issued by the FDA [4].

Most xenotransplantation products are from porcine origin, despite the fact that the general definition is much broader, i.e., including any cross-species transplantation. Originally, organs (kidney, heart) received most attention. A second category includes cells [5], mainly pancreatic islets given either by infusion of naked cells in the portal vein with subsequent lodging in the liver, or positioned after encapsulation at various locations like the subcutaneous space or the peritoneum, or administered in devices at various body locations that were implanted there prior to the cells. Xenogeneic islet transplantation has also been a focus of attention by the scientific community organized in the International Xenotransplantation Association (IXA) [6]. Decellularized tissue represents a third category [7]. This is a heterogeneous group of products, representing matrix scaffolds in tissue repair like heart valves and corneas, or scaffolds used in reseeding of cells in regenerative medicine.

The fact that the rejection of a xenogeneic (porcine) graft is more stringent than that of an allogeneic (human) graft, together with the progress in genetic engineering, has initiated attempts to genetically modify donor pigs. The first achievement, now 25 years ago, was a swine carrying a transgene of a complement regulator, with the result that naturally occurring anti-pig antibodies did not induce so-called hyperacute rejection [8]. Since then, a large spectrum of transgenes has been introduced, mainly to diminish immune reactions, coagulation and inflammation at the surface of porcine cells. Genetic modification has also been introduced to delete xenogeneic antigens to which human immune reactions are directed, so-called knock-outs [9]. The efficacy of these genetic modifications has been shown in transplantation of pig organs in nonhuman primates, a large animal model that closely resembles the pig-to-human transplant condition. A Xenotransplantation Consortium in Germany has recently contributed to this success by showing 195 days survival in pig-to-baboon orthotopic life-supporting heart transplantation [10]. The efficacy results, especially data on long-term survival, enabled the perspective of initiating clinical explorations [11], which was the topic of a joint symposium organized by the FDA and IXA in 2017 [12]. A third target for genetic engineering is of more recent date, namely the knock-out of genes encoding elements of porcine endogenous retrovirus (PERV) [13].

Regulatory agencies became interested in xenotransplantation when, about 25 years ago, certain pharma and biotech companies started xenotransplantation programs, with the claim to introduce porcine organs at large scale in clinical medicine. Also, around that time it was shown that in an in vitro cell culture model

PERV could productively transmit from a pig to a human cell [14]. This raised concern about safety of a xenotransplantation product, i.e., the potential of transmission of infectious agents from the pig donor graft into the human recipient, subsequently causing disease, not only in the recipient but also in relatives or even the human population. This not only regarded exogenous pathogens but also endogenous agents like PERV. Advisory committees within the government were established in the UK (United Kingdom Xenotransplantation Interim Regulatory Authority, UKXIRA, in existence between 1997 and 2006) and USA (Secretary's Advisory Committee on Xenotransplantation, SACX, in existence between 1999 and 2005). In Europe, the establishment of UKXIRA was related with the focus of Imutran Ltd (a Novartis Pharma AG Company since 1996) to advance their research to clinical development. After Novartis left the field in 2000 [15], UKXIRA reduced its activities. Related to these activities, groups in the UK issued seminal evaluations of xenotransplantation ethics [16, 17]. Within the SACX a draft informed consent form was developed in 2004 which is nowadays available at the website of the IXA [18]. The first documents issued by regulatory agencies (Guidances by FDA or Guidelines by EMA), in particular from the FDA, addressed this safety aspect [4, 19]. Also, the WHO issued a Guidance at that time (2001) [20] and subsequently organized Global Consultation meetings, the third one in 2018 [21]. Already in 2004 the WHO expressed its concern in a resolution requesting proper control by regulatory agencies when using xenotransplantation products in clinical medicine [22].

In Europe, the EMA has issued a Guideline in 2009 focusing on the microbiological safety of cell therapy products [23]. In the following, the global regulatory approach in various topics of xenotransplantation oversight will be described focusing on the European Union, e.g., the approach by the EMA.

Regulation of Xenotransplantation

Medicinal Products in Europe

In Europe, xenotransplantation products for use in humans are considered a medicinal product. In line with Directive 2001/83/EC, the products fulfill one of the requirements for the substance: mico-organisms, whole animals, part of organs, animal secretions, toxins, extracts, blood products [24]. Following this consideration, xenotransplantation products are considered an advanced therapy medicinal product (ATMP), for which a Regulation was issued in 2007 [25]. ATMPs are medicines for human use that are based on genes, tissues or cells, and are classified in three main types [26, 27]:

- gene therapy medicines: these contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases,

- somatic cell therapy medicines: these contain cells or tissues that have been manipulated to change their biological characteristics, or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases,
- tissue-engineered medicines: these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue,
- combined ATMP, e.g., an ATMP covered in a medical device. Some ATMPs may contain one or more medical devices as an integral part of the medicinal product, which are referred to as combined ATMPs. An example of this is cells embedded in a biodegradable matrix or scaffold.

There are three main categories of xenotransplantation products: cell therapy products, organ transplants and decellularized products/scaffolds. These are described in more detail below.

Regulatory Oversight

Regarding medicinal products, globally, regulatory agencies are well equipped to address chemistry-based compounds and extraction-based biological compounds. The process in evaluation of new medical entities and its follow-ups is well established, e.g., by a large series of Guidelines issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) that in part overlap with, or were followed by, documents issued by regulatory agencies [28]. This broad experience is less for product types that are of more recent date (i.e., last decades) in discovery and development, like ATMPs. For instance, the number of ATMPs that are nowadays on the market is quite limited: in 2018 there were 10 ATMPs approved for market authorization in Europe [29] which is discussed further below.

It is evident that the process and procedures used in evaluation of chemicals and biologicals do not apply for xenotransplantation products but require a different approach in oversight. From a philosophical view, such a regulatory approach is immensely difficult to establish: a simple (low molecular weight) chemical substance is very well characterized, while the product characterization is already causing problems for high molecular weight recombinant proteins with intrinsic variations, and almost impossible for cells that produce a huge variety of factors dependent on the environment in which they reside, and even can evolve becoming dangerous in the host (e.g., malignant transformation). Extending this to an organ, the question can be raised of how to control organ activities besides those intended to function properly in replacing the deficiency, i.e., organ activities that are either not known or not controllable. Essentially, presently used methodology in testing chemicals, or even recombinant proteins, cannot be applied, and results of clinical trials or long-term evaluation after market entry are awaited to learn more about these aspects. In part, the use of surrogate markers could contribute to solving these issues, being intrinsic to the nature of innovative products.

Regulation: Safety

Regarding xenotransplantation products, regulatory authorities have mainly addressed the safety aspects associated with transmission of infectious pathogens. The possibility of cross-species transmission of PERV mentioned in the section "Introduction" above resulted in a letter from the FDA in 1998 stating that clinical trials should be put on hold until adequate monitoring strategies are developed and implemented [30]. Subsequently, FDA issued a Guidance, which after some revisions in 2016 is still in place [4]. This Guidance applies to all xenotransplantation products, irrespective of the category mentioned in the section "Medicinal Products in Europe", and describes, amongst others, the way in which donor animals should be generated in high-hygiene conditions (designated pathogen-free, DPF). The Guidance does not present lists of pathogens that should excluded in the donor herd: such lists are published by the scientific community [31–34].

Regulation: Efficacy

Regulatory agencies have not issued detailed requirements regarding efficacy assessment. This is understandable because such requirements might be different for the different categories of products mentioned in the section "Medicinal Products in Europe", while safety aspects related to cross-species transmission of infectious pathogens is more universal. Also, efficacy features are indirectly associated with those of the human equivalent after replacing the deficient organ/tissue/cells by a porcine-derived product. There is one item that is not always considered, namely the physiological compatibility between the same organ/tissue/cell in a pig and a human. This was addressed already in the early days three decades before in exploratory comparisons for kidney and heart [35–37], and in more detail recently for islets [38]. This aside, regulatory agencies evidently require efficacy data in judgement of xenotransplantation products in the application of phase transition from nonclinical to clinical development, but do not define the respective specifications. It is realized that this requires a case-by-case approach, including a product-related appropriate animal model. This approach often requires discussion with the regulatory agencies about selecting the model and the study protocol. The preferred animal model differs between the various continents on earth: e.g., models in nonhuman primates seem still preferred in USA while this is not a preference in Europe. Also, for a first cornea xenotransplantation product in Korea nonclinical data in a nonhuman primate model were proposed [39]. The rationale for selecting nonhuman primates is the close similarity with humans in structure and function of the immune system including aspects of sensitivity to immune suppression (especially biologicals), and similarities in organ physiology. But, in Europe there is a strict Directive (i.e., not a Guideline) regarding research in nonhuman primate species [40]; unlike the situation in, e.g., the USA, there is no longer in Europe a widespread availability of centers where research in nonhuman primates is conducted. For some xenotransplantation products like cell therapy products, it has been proposed in

communications with regulatory experts to use animal models in rodents with properly designed studies addressing efficacy and safety (unpublished communications).

Regulation: Genetic Modification

Interestingly, changing from natural (wild-type) animals to genetically modified animals changes the picture on efficacy data. The best illustration comes from the FDA-IXA symposium mentioned above [12]: the genetic modification of an animal purposed to provide a xenotransplantation product requires not only data on normality in life of animals, e.g., during breeding and holding including animal welfare, but also the efficacy of the component inserted by transgenesis or the component deleted in a knock-out procedure. In other words, the product of genetic modification is considered a medicinal product. In practice, this might present a complication for complex modifications including multiple transgenes or knock-outs (in recent studies up to 10 [9]), when it is required to provide data separately for each individual component. First, just like in conventional approaches requiring multiple drugs (chemical compounds and/or biologicals), there is often synergy between the individual components and the assessment of each single component which requires multiple costly experiments in animal models. Second, even more important, the basic of a "drug" in genetic modification is nowadays a gene sequence combining multiple transgenes or knock-outs which cannot be separated from each other. Also, synergy assessments requiring different dose levels of individual components cannot be performed. There is not yet a solution reported for this potential complication by regulatory agencies, e.g., in proper Guidelines or Guidances, but the item is relevant if efficacy needs to be demonstrated for each individual component in a genetic modification.

Nowadays, there is detailed regulation of genetically modified organs in place, within Europe a specific Guideline [41]. Issues for consideration include the donors of xenotransplantation products, in which the focus is on the description of the genetic constructs, generation of genetically modified animals, husbandry and animal welfare, persistence of the synthesis and function of gene products in successive generations, special procedures in disposal of animal remains and materials (including but not limited to use of materials elsewhere like in clinical applications), assurance that there is no entrance of materials in the food chain, and respective record-keeping and reports.

Archiving and Storage of Materials

The focus of regulatory assessment on microbiological safety is considering not only a potential disease in the individual patient due to a pathogen acquired by a xenogeneic transplant, but also the subsequent spread among relatives and the population in general (i.e., safety is a public health issue). To this end regulatory

authorities demand that the recipient of a xenotransplantation product consents to a lifelong monitoring, donation of biological test samples, and finally a necropsy after death. Also, materials from the porcine donor and the human recipient should be stored for substantial periods (including storage of cells in liquid nitrogen), i.e., 50 years according to documents from US agencies [19] and 30 years in the EU ATMP Regulation [25]. This requirement asks for substantial financial investments by the sponsor of the trial and can only be resolved, especially regarding the logistics, in agreement between sponsor, the human recipient, and the respective governmental health institutions. There are no reports in literature whether and how a solution was achieved. This may be except for the situation in Switzerland, where clinical transplantation is overseen by law [42] and the government has issued an Ordinance on clinical xenotransplantation in which it is stated that the samples mentioned above should be made available to cantonal authorities [43].

Informed Consent

Clinical trials require an informed consent from the subject (or their surrogate) receiving the test material, and this is even more the case for a recipient of a xenotransplantation product [18]. Xenotransplantation-associated aspects include, as stated above, the consent of lifelong monitoring and agreement to an autopsy after death, which is in apparent contrast to the right of the patient to withdraw from a clinical trial without further consequences [44]. In a commentary on the first life-saving xenogeneic heart transplant in early 2022 a potential solution for this issue was proposed, namely the informed consent to be written as a Ulysses contract [45]. A Ulysses contract is a document by which one person binds himself by agreeing to be bound by others. In medicine such contracts have primarily been discussed as enabling to treat people with episodic mental illnesses, where the features of the illness are such that they now judge that they will refuse treatment at the time it is needed [46, 47].

Xenogeneic Cell Transplantation

Considering allogeneic islet transplantation, there was no regulatory oversight in place when the first transplants of human islets entered clinical medicine. Although logically being considered an ATMP, human islets received an exempt situation after the ATMP regulation was established [48]. As a consequence for xenogeneic cells, regulatory oversight cannot be just copied from the conditions for human islets [49].

Essentially, in Europe a substantial series of Regulations, Directives and Guidelines have been issued after the basic ATMP regulation 1394/2007 [25] that apply to the regulatory oversight of cell therapy products (called cell-based medicinal products, CBMP), being either autologous, syngeneic, allogeneic or xenogeneic (Table 10.1) [50]. In addition, the Guideline on genetically modified materials mentioned above has to be considered if applicable [41].

Table 10.1 Cell-therapy and tissue engineering: relevant EMA guidelines

Cell-therapy and tissue engineering	• The *overarching guideline* for human cell-based medicinal products is the guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006) • Reflection paper on *stem cell-based medicinal products* (EMA/CAT/571134/2009) • Reflection paper on in vitro cultured *chondrocyte* containing products for cartilage repair of the knee (EMA/CAT/CPWP/568181/2009) • Guideline on *xenogeneic cell-based medicinal products* (EMEA/CHMP/CPWP/83508/2009) • Guideline on potency testing of *cell based immunotherapy medicinal* products for the treatment of cancer (CHMP/BWP/271475/06) • Reflection paper *on clinical aspects related to tissue engineered products* (EMA/CAT/573420/2009) • Guideline on *safety and efficacy follow-up and risk management* of advanced therapy medicinal products (EMEA/149995/2008)
Gene therapy	• Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP) (EMA/CAT/499821/2019) • Quality, non-clinical and clinical aspects of medicinal products containing *genetically modified cells* (CHMP/GTWP/671639/2008)
Biologicals: drug product	• Guidance on the *use of bovine serum* in the manufacture of human biological medicinal products (CPMP/BWP/1793/02) • *Minimising the risk of transmitting animal apongiform encephalopathy agents* via human and veterinary medicinal products (EMA/410/01) • CHMP/CAT position statement on *Creutzfeldt-Jakob disease* and advanced therapy medicinal products (CHMP/CAT/BWP/353632/2010) • Position paper on re-establishment of *working seeds and working cell banks using TSE compliant materials* (EMEA/22314/02) • Guideline on the *use of porcine trypsin* used in the manufacture of human biological medicinal products (EMA/CHMP/BWP/814397/2011)
Biologicals: drug substance	• Note for guidance on *plasma derived medicinal products* (CPMP/BWP/269/95)
Quality: excipients	• Guideline on *excipients* in the dossier for application for marketing authorisation of a medicinal product (EMEA/CHMP/QWP/396951/2006)
Quality: ICH	• ICH Q2 (R1) validation of *analytical procedures*: text and methodology (CPMP/ICH/381/95) • ICH Q5A (R1) viral safety evaluation of *biotechnology products derived from cell lines* of human or animal origin (CPMP/ICH/295/95) • ICH Q5C stability testing of *biotechnological/biological products* (CPMP/ICH/138/95) • ICH Q5D derivation and *characterisation of cell substrates* used for production of biotechnological/biological products (CPMP/ICH/294/95) • ICH Q5E comparability of *biotechnological/biological products* (CPMP/ICH/5721/03) • ICH Q7 good manufacturing practice for *active pharmaceutical ingredients* (CPMP/ICH/4106/00) • ICH Q8 (R2) *pharmaceutical development* (CHMP/ICH/167068/04) • ICH Q9 *quality risk management* (EMA/CHMP/ICH/24235/2006) • ICH Q10 *pharmaceutical quality system* (EMA/CHMP/ICH/214732/2007)

(continued)

Table 10.1 (continued)

Safety: ICH	For non-clinical specific guidance, see • ICH S6 (R1) preclinical safety evaluation of *biotechnology-derived pharmaceuticals* (CHMP/ICH/731268/1998)
Safety and efficacy: Biostatistics	• Guideline on *clinical trials in small populations* (CHMP/EWP/83561/2005) • Points to consider on applications with *1. Meta-analyses; 2. One pivotal study* (CPMP/EWP/2330/99)
Efficacy: ICH	• ICH E1 the extent of population *exposure to assess clinical safety* (CPMP/ICH/375/95) • ICH E3 structure and content of *clinical study reports* (CPMP/ICH/137/95) • ICH E4 dose response information to support *drug registration* (CPMP/ICH/378/95) • ICH E6 (R1) *good clinical practice* (CPMP/ICH/135/95) • ICH E7 *geriatrics* (CPMP/ICH/379/95) • ICH E8 general considerations for *clinical trials* (CPMP/ICH/291/95) • ICH E11 clinical investigation of *medicinal products in the paediatric population* (CPMP/ICH/2711/99)
Clinical safety and efficacy	*Existing clinical guidance* for the studied indication(s) should be consulted.
European Pharmacopoeia	The following monographs from the European pharmacopoeia (Ph. Eur) should be considered, where relevant: • Ph.Eur. monograph on *human haematopoietic stem cells* (Cellulae stirpes haematopoieticae humanae) version 7.2 • Ph.Eur. monograph on method of analysis (2.7.23.) *numeration of CD34/CD45+ cells in haematopoietic products*. Version 7.2 • Ph.Eur. monograph on method of analysis (2.7.28.) *Colony-forming cell assay for human haematopoietic progenitor cells*. Version 7.2 • Ph.Eur. monograph on *Nucleated Cell Count and viability* (2.7.29.) • Ph.Eur. monograph on *Nucleic Acid Amplification Techniques* (2.6.21.) • Ph.Eur. monograph on *flow cytometry* (2.7.24.) • Ph.Eur: (2.6.27) *microbiological control of cellular products* • Ph.Eur: (2.6.1.) *sterility* • Ph.Eur: (5.1.6) *alternative methods for control of microbiological quality* • Ph.Eur. monograph *Mycoplasmas* (2.6.7.) • Ph.Eur. monograph on *bacterial endotoxins* (2.6.14.) • General chapter 5.2.12 raw materials for the production of cell-based and gene therapy medicinal products

Data from reference [50]
ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

A complex situation exists for the regulation of cells that are encapsulated. Since the optimal way of administration has not been established, and the need for protection from the local environment mediating destruction by immune and inflammatory reactivity was recognized, encapsulation has been introduced to facilitate ongoing function of the cells after transplantation. Two main tools have been introduced in research endeavors: (1) encapsulation in vitro using molecules, mainly alginate-based, that form hydrogel microspheres in an electrostatic network or covalent bonding, or (2) insertion in devices that are implanted at location and adapted to the local environment before administration of the cells. Generally, the encapsulated cells in the capsule are considered the product (the active pharmaceutical ingredient) and the encapsulated product is considered a combined ATMP, while in the second situation the naked islets are considered the xenotransplantation product independent of how the device is constructed and implanted. Evidently, this is because device-specific regulations are in place, which are not discussed here.

Xenogeneic Solid Organ Transplantation

It is not possible to translate regulatory oversight of a human solid organ to the situation of a xenogeneic solid organ transplantation product. This is because a human organ for transplantation, irrespective of the donor (e.g., a deceased individual or a living organ donor, a patient's relative), is not considered a medicinal product, because it fulfills the condition that the material is not substantially modified and/or exerts the same essential function in donor and recipient (i.e., homologous use). In Europe, human organ transplantation is defined as follows: "Human organ transplantation is the therapeutic use of human organs as a substitute for one that is nonfunctional. The organ may come from a deceased or a living donor" [51]. Human organ transplantation is overseen by regulatory agencies in each individual member state according to Directive 2010/45/EU [52], which is transposed into national legislation. A more detailed guideline concerning, for example, infectious risks, has been issued by the European Directorate for the Quality of Medicines & HealthCare [53].

Hence, although a solid organ was the apparent initiative for regulation of xenotransplantation products, there is no specific regulatory oversight established for a solid organ xenotransplantation product. This situation is even more complicated since solid organs are to be considered an ATMP, and many associated regulatory requirements in the network of Regulations and Directives do not easily apply to solid organs. This issue especially regards product quality for which requirements

associated with the ATMP status differ from those for a human transplant: noteworthy, human organs themselves used for transplantation are not subject to quality testing like is done in release of medicinal products.

In this discussion it should be realized that xenogeneic donors provide unique opportunities for product characterization and quality assessment that is not possible for their human equivalents. Such testing includes aspects of functional quality and consistency of parameters that are together with others normally part of quality assessment and release of medicinal products. In this view, a xenogeneic solid organ is fundamentally different from the organ of a human donor. Elsewhere this point is addressed in more detail [54] in relation to the flow chart of the process starting with the selection of an animal in the source facility and ending with the delivery of the solid organ product in the clinical transplant center (Fig. 10.1). Table 10.2 summarizes the main activities at the distinct locations in this flow chart as well as a proposal for the quality systems to be applied at each site for a solid organ from a (genetically modified) animal.

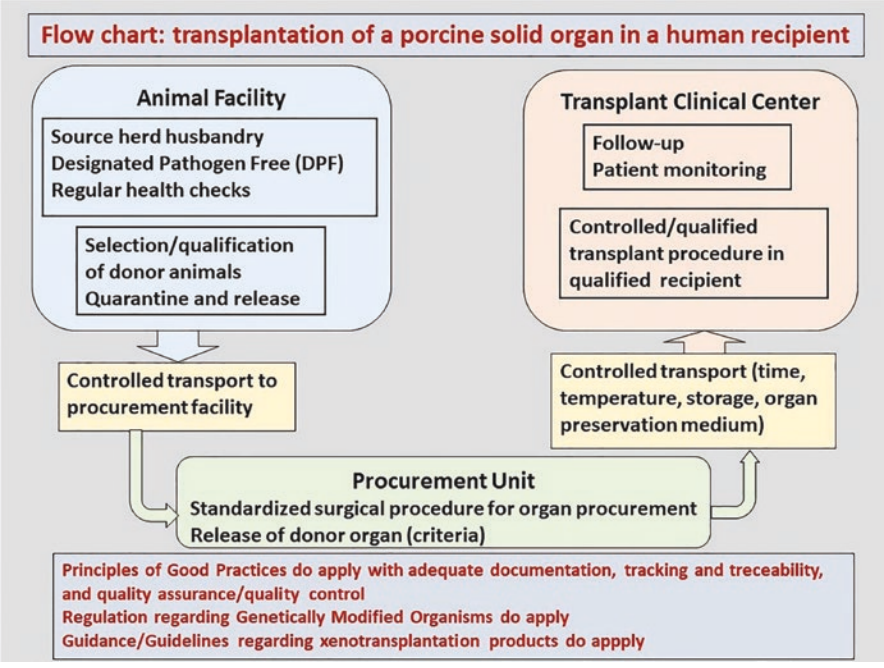

Fig. 10.1 Flow chart of the generation of an organ from a (genetically-modified) pig for transplantation in a human recipient. The three main locations are depicted, i.e., the animal facility, the procurement unit and the transplant clinical center, and the transport in between of the donor pig and the procured organ. Also the regulatory oversight of activities in this flow chart are summarized. Reproduced from reference [54], with permission

Table 10.2 Key activities in the process of a xenotransplantation clinical trial with an organ procured from a (genetically-modified) pig

Key activity[a]	Source animal	Organ procurement	Clinical application (transplantation)
Material acceptance (begin)	Herd health status and monitoring	Acceptance animal: macroscopic inspection according to GLP	Acceptance organ: macroscopic inspection
Quality management system	"Good husbandry practices"	"Good procurement practices"	Patient eligibility and selection: Informed consent Transplant functionality as part of routine follow-up according to GCP
Risk evaluation and management	Supply of animal	Supply of organ	Cross-species infection and physiologic incompatibilities
Quality control (end)	Release criteria: microbial safety (post release) Organ functionality according to GLP	Release criteria: microbial safety (post release) Organ inspection according to GMP	Monitoring for cross-species transmission post administration Archiving of tissue/cells Option for human transplant
Transport	Transport security	Shipment security according to GDP	N/A
Responsibility	Provider (husbandry)	Procurement organization	Principal investigator (responsible personal) at clinical center

Reproduced from reference [54], with permission
GCP Good clinical practices, *GDP* Good distribution practices, *GLP* Good laboratory practices, *GMP* Good manufacturing practices, *N/A* Not applicable
[a] Precludes regulatory oversight for distinct activities

Decellularized Products

Decellularized products include a scaffold in repair of tissue or scaffold in regenerative medicine for reseeding by autologous cells [55]. If the tissue is not containing viable cells, it is a xenograft and not a xenotransplantation product, and essentially a medical device as described in the section "Introduction". This situation is independent of the fact whether the donor animal is genetically modified or not. For any other condition, i.e., when the tissue contains viable cells, is reseeded with autologous cells, or is transplanted as fresh tissue after decellularization, the product is considered an ATMP. Considering the huge variability and in the absence of product-specific regulation, regulatory oversight evidently needs to be done on a case-by-case basis.

The Role of the European Medicines Agency

Within the European Union, each member state has its regulatory agency that oversees the development and use of medicinal products. For ATMPs a centralized process has been established in which the development, from advanced research to

market authorization, is overseen by EMA [56]. This central authorization of ATMPs via the EMA seems logical considering the huge variability in composition between products with its consequence for the CMC (Chemistry, Manufacturing and Control) part in product overview, and considering the low numbers of ATMPs proposed for clinical development requiring special expertise within the respective regulatory agency. There is flexibility in the routes toward market authorization, i.e., a first and subsequent contacts with regulators can be with a country-based agency. This includes scientific advice for items where the country-based agency has specific experience: an example is the Paul Ehrlich Institute in Germany, which is the competent authority for this group of medicines in Germany [57]. To illustrate this, staff of the institute conduct research in the field which includes xenotransplantation as illustrated by a reference [55].

Central in the oversight of ATMPs is the Committee for Advanced Therapies (CAT) [58]. The main responsibility of this committee is to prepare a draft opinion for each ATMP application submitted to EMA, before the Committee for Medicinal Products for Human Use (CHMP) prepares a final opinion on the marketing authorization. The activities of CAT span a wide range and include, amongst others, classification of a new product for the status as ATMP [27, 59], and scientific advice at various stages of the development process [60, 61]. CAT also organizes workshops on various topics related to development of ATMPs [62, 63]. All aspects in development, illustrated by the network of Regulations and Directives (Table 10.1) [50], are considered in the evaluation of ATMPs during development, in contacts between sponsor and CAT.

As stated in the section "Regulatory Oversight" the number of ATMPs that received market authorization in Europe is rather low, i.e., 10 in 2018, and this low number is at first view related to the high costs in production and/or small target patient populations. This low number prompted a survey among companies involved with development of ATMPs aiming to identify challenges experienced in ATMP development [29]. This survey published in 2018 included 68 companies out of a total of 271 companies that were approached, the majority being small- and medium-sized enterprises (SMEs) (65%). The results showed that challenges were quite variable, most often related to country-specific requirements (16%), manufacturing (15%), and clinical trial design (8%).

The low number of ATMPs that made it to market also prompted regulatory authorities to develop support programs. The Directorate General Health and Food Safety of the European Commission together with EMA initiated a number of initiatives to improve the regulatory environment for ATMPs thereby facilitating the development and authorization of ATMPs in the EU for the benefit of patients [64]. As part of this supportive action, EMA has included in the section "Guidance on ATMP Development" of the overview page on ATMPs [26] checklists and flowcharts for preclinical and clinical development, and for quality of products in development: an extract of most important requirements for the preclinical and clinical development, and for quality, is presented in Tables 10.3, 10.4 and 10.5.

Table 10.3 The most important regulatory requirements during the preclinical development phase of cell-based medicinal products (EMA, ATMP)

What are the potential risks associated with the clinical use of ATMP	Perform a risk based approach, including addressing any safety concerns from previous clinical studies of similar products
What is the intended patient population?	Identify specific patient eligibility criteria based on safety, pharmacokinetic and efficacy data
What are the toxicological and safety effects?	Perform general safety and toxicity studies, including studies based on risk-based approach
What is the therapeutic window? What should be the starting dose and dosing scheme in humans	
What is the efficacy? What is the mechanism of action?	Carry out a proof of concept study
What are the pharmacokinetic characteristics?	Perform a pharmacokinetic study investigating, among others, distribution and persistence Investigate the inadvertent germline transmission

Data from reference [26]

Table 10.4 The most important regulatory requirements during the clinical development phase of cell-based medicinal products (EMA, ATMP)

Does the drug reach the site of action?	Investigate the feasibility of the route of administration and pharmacokinetic characteristics such as biodistribution and elimination
Does the compound cause its intended pharmacological effects? And what are the undesired pharmacological effects?	Demonstrate the mechanism of action and off-target pharmacological effects
Does the compound have Beneficial effects on the disease or its pathophysiology?	Investigate the effect on The disease and relevant Pathophysiological systems
What are the sources of variability in drug response in the target population?	Determine sources of variability in Drug response (e.g. concomitant Medication, disease status, prognostic factors) and if dose adjustment is required
What is the therapeutic window?	Determine the starting dose of the first in human study and determine the optimal dose regimen based on all safety and efficacy data
Are there off-target Pathophysiological effects?	Investigate safety and tolerability

Data from reference [26]

Table 10.5 The most important regulatory quality-related requirements of cell-based medicinal products (EMA, ATMP)

Is the development of the potency assay on schedule?	Perform a potency study
Are the products comparable across all studies Will future changes in the manufacturing process (including upscaling) or product be needed?	Consider a comparability exercise Describe control strategy of materials and manufacturing process
What is the location of the manufacturing site	Ensure the manufacturing adhere to the Suropean GMP regulations Read the rules that apply to importing products into the EU after production outside EU
Have you started preparing the marketing authorization dossier	Define the active drug substance and the final drug product and determine if it is a new active substance Identify raw materials and starting materials Check the community register of orphan medicinal product to see if a similar medicinal product for the same therapeutic indication has been granted market exclusivity protection

Data from reference [26]

Conclusions and Perspectives

After incidental transplants in the past, xenotransplantation received a boost three decades ago, combining then newly available immunosuppressants with genetic modification of animals some years later. Today, the field has made substantial breakthroughs and periods of stabilization like any other young discipline in medicine. For xenogeneic encapsulated islets a small clinical trial has been conducted in New Zealand [33, 65], for which a long process proved necessary to receive Ministerial approved [6]. In the first days of 2022, a first-in-human exploratory study was conducted with a heart from a pig with 10 gene modifications in a patient with terminal heart failure [66]. This study was approved by the FDA [67, 68] following the conditions of expanded access ("compassionate use") [69]. Earlier, the FDA approved a phase 1/2 clinical trial testing vital skin from miniature swine with 1 gene knock-out modification in patients with severe burn [70, 71].

Market entry of xenotransplantation products has not yet been realized. In Europe, clinical trials have not yet been initiated, but a number of groups have been in Scientific Advice meetings with regulatory agencies discussing products at the advanced nonclinical level.

Xenotransplantation products are innovative and new for regulators [72]. Today there is a spectrum of regulatory documents, which form the basis for clinical trial applications by sponsors of ATMPs. Most of these regard safety, i.e., the risk of transmission of endogenous or exogenous infectious pathogens. Noteworthy, with

the exception of a Guideline for xenogeneic CBMPs [23], there is no regulatory document that specifically addresses xenotransplantation products. For CBMPs the presently available regulatory oversight developed for autologous, syngeneic and allogeneic cells seems suitable to provide oversight for these xenotransplantation products, but oversight of xenogeneic organs might request additional regulatory documentation.

Since there is very little experience in evaluating xenotransplantation products by regulatory agencies, mutual experience needs to be built with sponsors, in which in-depth discussions between the parties, regulators and sponsors, are needed and highly recommended. Besides IXA [12] the International Society for Cell & Gene Therapy should be mentioned as medium in these translations, considering the mission of this society [73]. Xenotransplantation products are complex regarding their oversight, and the complexity regards not only efficacy and safety but also compatibility in physiology and function. This latter point has received little attention but needs to be addressed in studies preparing for clinical trials, and later market entry. Experience in long-term survival of porcine islets in diabetic monkeys serves to illustrate this issue [38].

There are a number of points that need discussion between regulators and sponsors. One of these regards the potential transmission of endogenous infectious agents: this is not only of relevance for the patient receiving a xenotransplantation product, but also is a potential public health issue. To this end, lifelong patient monitoring and storage of samples from porcine donor and human recipient has been requested. The logistics in realizing this demand needs discussion between sponsor, potential human recipients, and health institutions.

Besides these complexities, xenotransplantation has still many opportunities to bring innovative new medicinal products to clinical medicine. There have been—and still are—hurdles in development, and there might be still a long way to go, but with the present perspectives to initiate or perform exploratory clinical trials there are major achievements anticipated.

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Conflict of Interest Henk-Jan Schuurman is director at SchuBiomed Consultancy and provides consultancy in the biomedical sector worldwide.

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