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The Challenge of Public Participation in a Multilevel System: EU Xenotransplantation Policies

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Founded in 1963 by two prominent Austrians living in exile – the sociologist Paul F. Lazarsfeld and the economist Oskar Morgenstern – with the financial support from the Ford Foundation, the Austrian Federal Ministry of Education, and the City of Vienna, the Institute for Advanced Studies (IHS) is the first institution for postgraduate education and research in economics and the social sciences in Austria. The **Sociological Series** presents research done at the Department of Sociology and aims to share "work in progress" in a timely way before formal publication. As usual, authors bear full responsibility for the content of their contributions.

Das Institut für Höhere Studien (IHS) wurde im Jahr 1963 von zwei prominenten Exilösterreichern – dem Soziologen Paul F. Lazarsfeld und dem Ökonomen Oskar Morgenstern – mit Hilfe der Ford-Stiftung, des Österreichischen Bundesministeriums für Unterricht und der Stadt Wien gegründet und ist somit die erste nachuniversitäre Lehr- und Forschungsstätte für die Sozial- und Wirtschafts-wissenschaften in Österreich. Die **Reihe Soziologie** bietet Einblick in die Forschungsarbeit der Abteilung für Soziologie und verfolgt das Ziel, abteilungsinterne Diskussionsbeiträge einer breiteren fachinternen Öffentlichkeit zugänglich zu machen. Die inhaltliche Verantwortung für die veröffentlichten Beiträge liegt bei den Autoren und Autorinnen.

Contents

1 Introduction

1.1 Main Project Objectives

Citizens, policymakers and social scientists often call for citizen participation for reasons of democratic legitimacy and effectiveness. A field in which this has been vigorously asserted is science and technology policy. Many countries therefore witnessed the introduction of Participatory Technology Assessment (PTA). The "litmus test" of PTA and of citizen participation, however, is their impact on policy making. But can PTA keep its promises and increase the influence of citizens' voices on decision-making? What is in actual fact the impact of PTA on decision-making? How can it be increased?

In order to answer these questions the project "Impact of Citizen Participation on Decision Making in a Knowledge Intensive Policy Field" *(CIT-PART)* comparatively studies the impact of PTA and expert based technology assessment (TA) on policy making in Austria, Canada, Denmark, Italy, Latvia, The Netherlands, Sweden, Switzerland, United Kingdom, the European Commission, the Organization for Economic Co-operation and Development (OECD) and the Holy See. From these the project draws conclusions about the possible impact of institutionalized citizen participation at European Union (EU) level.

The project addresses these questions through the reactions of various political systems to the challenge of xenotransplantation, which stands for the transplantation of animal organs, tissues or cells into humans. Xenotransplantation is highly controversial: its advocates perceive it as promising since it could help to remedy the shortage of human transplants, while its opponents insist that it involves too many risks - most prominently infection from animals to humans - and ethical questions.

By adopting a theoretical approach of “social practices”, this project starts from the assumption that the impact of citizen participation on decision-making is not only dependent on the quality of the PTA process itself but on practices of policymaking in which PTA is embedded. Following from this theoretical approach, the project applies qualitative methods of empirical research.

1.2 Case Selection

Since the mid 1990s the European Institutions and the European Agency for the Evaluation of Medicinal Products (EMEA)[1] adopted diverse xenotransplantation policies (see Table 1). On the one hand they financed and enabled xenotransplantation research through various

[1] The European Agency for the Evaluation of Medicinal Products was renamed in 2004 into European Medicines Agency (Regulation 726/2004). We will use the unofficial abbreviation EMA for the European Medicines Agency and EMEA for the European Agency for the Evaluation of Medicinal Products.

measures. The European Commission, e.g., has been funding xenotransplantation research since its 4th Framework Programme; in 2001 the European Commission's Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) formulated a cautious yet overall positive opinion concerning xenotransplantation; in 2003 the EMEA published "Points To Consider On Xenogeneic Cell Therapy Medicinal Products", addressing firms who might plan to apply for market authorization in this area; in 2009 the Scientific Committee on Health Environment and Risk (SCHER) adopted its Opinion "The need for non-human primates in biomedical research, production and testing of products and devices" (SCHER 2009), which identified xenotransplantation as one of a few research areas where the use of non-human primates was considered necessary. On the other hand, European Institutions also contributed to more restrained xenotransplantation policies. In 2001 the European Council, the European Parliament and the European Commission agreed on Directive 2001/20/EC, which enabled European Member States to postpone applications for clinical research on xenotransplantation without time limit. All these policies were based on expert advice and often explicitly excluded the consideration of social and ethical problems from the scope of its analysis. Policy making procedures as well as the procedural arrangements of expert committees left little space for citizen participation. However, there is also another facet to EU xenotransplantation policies. The European Commission did not only fund xenotransplantation research itself but also research into its ethical, legal and social aspects (ELSA). Moreover it supported research, which looked into the problem of how to involve stakeholders into debates about the ethics of xenotransplantation. This case study aims to look more deeply into these varied xenotransplantation policies.

The topic of public participation is particularly challenging for the European Institutions for several reasons. First, similarly to national governments, the European Institutions are highly complex bureaucratic organizations, which, as has already been shown, have to cover a wide range of policy fields. They therefore face problems of internal differentiation and coordination typical to complex organizations. The complexity of European Institutions, however, is significantly amplified because of the various, and to a certain extent contending, levels of European policy making (communal, regional, national, and European) and European Institutions (European Commission, European Council, and European Parliament). This complex relationship is particularly played out in the area of health policy, where competencies lie mainly with the European Member States. The case study identifies the opportunities for and obstacles to citizen participation in a multilevel system.

Against this background the main research questions of this case study are:

- Which xenotransplantation policies did European Institutions and the EMEA/EMA develop?
- Which actors were involved in what practices in the policy making processes?
- What role did experts and the public play in these processes?

In addressing these questions, we focus particularly on xenotransplantation policies around the turn of the millennium but will also address some later developments in the first decade of this century.

Table 1: Timeline and overview of landmark developments

1997		The European Commission starts funding xenotransplantation research projects.
1998	02	The SCMPMD mentions xenotransplantation as a subject that will become important in the future.
1999	09	The SCMPMD working group commences its work.
2000	03	"Life sciences and biotechnology – A strategy for Europe" identifies Xenotransplantation as an economically promising area.
2001	03	Directive 2001/18/EC on the deliberative release into the environment of genetically modified organisms is released.
	04	Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use is released. The Directive (updated by Directive 2005/28/EC) explicitly addresses the use of xenogeneic cell therapy.
	10	The SCMPMD adopts its Opinion on xenotransplantation.
	11	Directive 2001/83/EC on the community code relating to medicinal products for human use is released.
2000		The EMEA starts to work on a guidance on xenotransplantation.
2003	06	Directive 2003/63/EC amending Directive 2001/83/EC establishes regulatory oversight on xenotransplantation in the field of medicinal products by including xenogeneic cell therapy into its Annex I (Part IV).
2004	03	Regulation 726/2004 reforms the EMEA and lays down rules for the authorization, supervision and pharmacovigilance of medicinal products for human and veterinary use.
	06	The EMA adopts "Points to consider on Xenogeneic Cell Therapy Medicinal Products".
2007	09	The European Parliament urges the Commission to end the use of apes and wild-caught monkeys in research and to establish a timeline to replace all non-human primates (NHP).
	09	The Commission responds that using non-human primates is currently necessary and requests an Opinion from the European Commission's Scientific Committee on Health and Environmental Risks (SCHER).
2008	10	Regulation 1394/07 on advanced therapy medicinal products (ATMP) enters into force. The EMEA's Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion on the granting, variation, suspension or revocation of a marketing authorisation for the medicine concerned.
2009	01	The SCHER identifies xenotransplantation as an area where the use of NHP is necessary.
2010	01	Guideline on xenogeneic cell-based medicinal products replaces "Points to Consider on Xenogeneic Cell-Therapy Medicinal Products".
	11	Directive 2010/63/EU acknowledges that animals, including non-human primates, are needed for research purposes.

1.3 Methods

This report is based on expert interviews and document analysis. The documents analyzed include official documents from, e.g., the European Commission, the European Parliament, the European Council, the EMEA/EMA, the SCMPMD and the SCHER. Moreover, the report is based on a review of relevant literature on xenotransplantation policies, the European Institutions and the EMEA/EMA. The main sources of information were interviews with civil servants and researchers active in EU xenotransplantation policies. Interviews were conducted with four officials of the European Commission, one xenotransplantation researcher, three researchers who participated in various scientific committees advising the European Commission, and one scholar of jurisprudence (see 8.4). In addition, a written statement by the EMA, which was provided on request, was analyzed.

Out of the interviews, four were carried out face-to-face and five were conducted by telephone. They were based on a guideline shared by all CIT-PART partners, which was derived from the methodological guidebook and was adapted according to necessity, primarily according to the interviewee's role in EU xenotransplantation policies. Interviews lasted approximately thirty minutes to one hour; almost all of them were taped and fully transcribed. Transcripts and records were analyzed by qualitative methods (thematic analysis). Interviews were used to describe EU xenotransplantation policies and to examine social practices of policy making, technology assessment and citizen participation. In a first round of analysis, themes were identified in each interview. In a second round, these themes were compared across interviews and theories were synthesized. Thematic analysis was conducted with the use of Atlas.ti, a software tool specifically developed for qualitative analysis. Interviews are quoted within the text. The letter in brackets refers to the interview and the numbers refer to the relevant lines in the transcript. In case of the written statement, the number refers to the respective page.

1.4 Acknowledgements

We acknowledge the funding of this research project by the European Commission. Without this support our research would have been impossible. In addition we want to thank all interviewees for their willingness to participate in the project. Without their open support we would have been unable to write this report. We also want to thank Vera Akhmetova and Hanspeter Wielander for transcription as well as Alexander Lang for transcription as well as assistance for additional Internet recherché.

Authorship of this report is divided in the following way: Anna Pichelstorfer and Karina Weitzer did most of the Internet recherché and literature review; they identified interview partners and produced an initial draft version of this report. Peter Biegelbauer contributed to the chapter on EU policy making and commented on parts of the final report. Erich Griessler did additional Internet and literature recherché, carried out and analyzed expert interviews,

made the overall concept of the report, extended and deepened analysis and wrote the final version of this report.

1.5 Layout of the Paper

The paper starts with an analysis of the scientific advice of the SCMPMD to the European Commission (chapter 2) and continues with a brief chapter on xenotransplantation as a promising economic research area (chapter 3). Chapter 4 describes the development of the regulation of xenotransplantation from the Directive on clinical trials to points to be considered by potential applicants for market authorization. Chapter 5 focuses on the use of non-human primates in research in the context of xenotransplantation. Chapter 6 discusses the European Commission's role in research funding, both in xenotransplantation itself as well as in ELSA research and citizen participation. The concluding section (chapter 7) recapitulates the main findings by addressing the central research questions of the CIT-PART project. The Annex provides a timeline of major developments, an overview of the political system of the EU and the policy field, as well as lists of references, interviewees and abbreviations.

2 The SCMPMD

The European Commission's Health and Consumer Protection Directorate-General[2] was one of the first divisions within the Commission to deal with xenotransplantation policies.[3] In February 1999 the then recently established Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) took initiative and brought up the issue as one of several topics which might become interesting for its future activities. Later the same year the SCMPMD decided to prepare an Opinion on Xenotransplantation. The following section outlines the development and content of the Opinion and views this process in the context of the reorganisation of the European Commission's advisory system in health and consumer protection that occurred in the mid-1990s. This chapter also addresses the involvement of experts and the public in the drafting of the Opinion and its impact on further policy development.

2.1 Developing an Opinion

2.1.1 Reorganization to Regain Public Confidence

In order to understand the work of the SCMPMD it is helpful to look into the context of its establishment. In 1997 the European Commission faced the severe political crisis of the BSE (Bovine Spongiform Encephalopathy, mad cow disease) scandal and an associated loss of public confidence in EU regulation. An interviewee explained that, amongst other measures, the Commission responded to this crisis by carrying out a "big reorganization of the scientific basis of the Community legislation" (a: 42-43). The European Commission created eight Scientific Committees,[4] which would provide scientific advice "at the Commission's request (…) on matters relating to consumer health and food safety" (EC 1997: Article 2.3.). By setting up the new advisory bodies and strengthening their scientific basis – previous advisory bodies were mostly composed so as to represent Member States - the Commission aimed at reaching two objectives: to regain public trust and to provide the basis for "good legislation" (a: 38 - 41). In order to achieve these goals the Commission formulated three central guiding principles on which its new Scientific Committees should be based on, i.e. "excellence, independence and transparency" (EC 1997).

2.1.2 Scientific Committee without Regulatory Competencies

Most of the newly established Scientific Committees replaced existing Committees (EC 1997: Article 12). However, the SCMPMD was the only completely new one. Its task was to provide advice to the Commission on "scientific and technical questions relating to

[2] in the late 1990s DG XXIV, in the following for reasons of simplicity DG SANCO.
[3] For a short overview see Tallacchini 2002: 371 ff.; for a critique Tallacchini 2011.
[4] This structure of the Scientific Committees was reorganized in 2004 and their number was reduced to three (see chapter 5).

Community legislation concerning medicaments for human and veterinary use" (ibid.). In addition, it had to deal with "scientific and technical questions relating to Community legislation concerning medical materials and equipment" (ibid.). However, as an interviewee stated, the SCMPMD was a "more difficult Committee" (a: 184-185). In contrast to other scientific committees, it lacked the responsibility to give authoritative advice on regulatory matters because this competence was, and still is, the domain of the EMEA/EMA (see chapter 4.2.3). In addition, the creation of the SCMPMD could potentially lead to a conflict between European Institutions, since the EMEA/EMA was, and still is, under the control of EU Member States, whereas the SCMPMD advised the European Commission (a: 197-207). In order to avoid conflicts between the EMEA and the SCMPMD as well as Member States and the European Commission, the Decision which set up the Scientific Committees states that the SCMPMD should do its work "without prejudice to the specific competences given to the Committee for Proprietary Medicinal Products and the Committee on Veterinary Medicinal Products in the evaluation of medicaments" (EC 1997: Article 12). This lack of a mandate in the regulation of medicinal products and devices made it difficult to find topics for the SCMPMD's agenda. It was therefore more of a "prospective" than a regulatory committee (a: 198-199), "interested in future issues" (a: 258-262). Xenotransplantation, as will be described in this paper, was regarded as such a prospective issue.

2.1.3 Recruitment and Composition

Scientific Committees have a maximum of 19 members (EC 1997: Article 3.1), which are appointed by the Commission for a three years' term (ibid. Article 5). The members are selected following an open call for expressions of interests. This call also includes the criteria by which Committee members are selected. The selection procedures have to be transparent and are intended to result in the "most suitable applicants for appointment to the Committees". The Commission appoints members of Scientific Committees from a list of candidates, which is the outcome of this selection process. Their names are published (EC 1997: Article 3.3). Committee members have to be "independent of all outside influence" (ibid. Article 6) and must declare any conflicts of interest. As an interviewee recalled, the goal of this procedure is to get "the best independent (...) scientists" (a: 92 ff.), who should impartially represent only themselves rather than being instructed by Member States (c.f. a: 97-99, ibid. 162-163). Committee members mainly come from European universities and national research institutes but also from abroad. It is also possible that they are recruited from Ministries and in "exceptional cases (from) enterprises" (a: 92).

2.1.4 Working Procedure

Different Directorate Generals (DG) can request opinions from Scientific Committees. In working out opinions, the SCMPMD established working parties, which involved approximately five experts; some of these were members of the Scientific Committee, others were external experts.

The Scientific Committee appointed some of its members for the new working party. From this group a chairman was then appointed. The working party members next decided on key topics to be dealt with and identified external experts to cover the necessary competencies. External experts were identified from the committee members' own "scientific network": from a DG SANCO pool of external experts and from a literature review of experts (b: 110-114). The working party drafted its opinion throughout the course of several meetings, the progress of which was reported to the SCMPMD in plenary meetings . The Scientific Committee discussed the drafts (a: 311-315) and adopted a final version by holding a formal vote.

Despite the Scientific Committee's considerable autonomy, the European Commission played an important role in the SCMPMD. Firstly, several DGs were entitled to take initiative and ask for expert advice. Secondly, as the Commission Decision which established the Scientific Committees stipulated, the "Commission shall provide the secretariat of the Scientific Committees, the sub-committees and the working parties" (EC 1997: Article 9.2). Commission staff supports Scientific Committees in their work, e.g., by setting up agendas, inviting people, and writing minutes. DG SANCO staff also facilitated Working Group meetings (b: 117) by overseeing these tasks. Commission staff also adopted and approved agendas. Thirdly, in order to be useful to the Commission, the activities of Scientific Committee's had to be linked to its needs for advice by addressing topics which were relevant to the Commission. In summary, an interviewee described the European Commission's role as a management task, which involved the establishment of the Committees as such, the recruitment of "the best people, to make it work" and to ensure "that there is a relation between what they do and what the Institution wants" (a: 301-304).

2.1.5 Public

One of the aims for reorganizing scientific advice to the European Commission was the need to increase its transparency to the public. The Commission Decision, which established the new Scientific Committees, therefore stated, that "the agendas, minutes and opinions of the Scientific Committees shall be published without undue delay and with regard being had to the need of commercial confidentiality. Minority opinions shall always be included and shall be attributed to members only at their request" (EC 1997: Article 10). The fact that, minutes of plenary sessions, opinions and a report about their policy impact were published on the Internet, certainly contributed to this aim. However, the transparency aimed for was considerably curtailed by the fact that the minutes published were very brief and comprised of only a participant list, an agenda and a short summary of discussion results. They did not provide much detail about the actual content of discussion, let alone different opinions expressed. More importantly, draft papers and minutes of working parties, where the main work was done, were not put on the Internet at that time. The one page report about the Opinion's policy impact is rather sparing of words (European Commission 2003: 24).

The next section leaves the general make up of the SCMPMD aside and focuses on the particular development of the Opinion on Xenotransplantation.

2.1.6 Development of the Opinion

The working party on xenotransplantation within the SCMPMD formulated its Opinion over a process of roughly two years, during which the issue was on the agenda in nine plenary meetings. The group met about ten times in Brussels to discuss the topic (b: 128).

In February 1999 at its 8th meeting, the SCMPMD Chairman, Dr. Jones, mentioned five subjects that might in the future appear on the Committee's list of items and asked the members to reflect on these issues. Xenotransplantation, among genetic therapy, live vaccines, tissue engineering as well as amalgam and other alloys for dentistry, was one of these issues listed in the minutes (SCMPMD 1999a).

Responding to the question of why xenotransplantation became a topic for the SCMPMD, an interviewee explained that Scientific Committees had "some room of competence" and were able to suggest topics that they wanted to look into (a: 63-65); for this purpose, committee members carried out, what another respondent called, "risk watch". They were "aware of the developments in (their) specific area, and then if new things pop up in that area, which might have an effect on public health, it will be brought to the attention of the Scientific Committee" (b: 57-59). This was also the case with xenotransplantation. The topic "was put onto the agenda (…) because scientists (…) wanted to put (it) onto the agenda" (a: 218-219). As another interviewee confirmed, xenotransplantation was "more or less self tasking from the Scientific Committee" (b: 85). It was on a list of "emerging issues" set up by the Committee itself, which might "become a risk for the health of the population" (b: 31-33) and was regarded as an issue of "relatively high risk" (b: 79). The immediate trigger was the release of a number of publications that dealt with clinical trials and the "continuous need for organ donors" (b: 71-74).

However, an issue had to pass several phases within the Committee in order to become topical. It first had to be raised, the Committee then had to agree and, finally, it had "to be brought to the attention of the Commission; they (had) to think about it" (b: 83-87).

At the 11th meeting in September 1999, two meetings after the issue was raised for the first time in the SCMPMD, a representative of the Council of Europe (CoE) Health Division was invited and informed about relevant discussions within the CoE by the Scientific Committee. He explained the aim and organisation of the CoE, , the organisational bodies involved in this topic,[5] as well as the principles[6] and legal tools[7] applicable in the case of

[5] Committee of Ministers, European Health Committee (CDSP), Steering Committee on Bioethics (CDBI), Working Party on Xenotransplantation (SCMPMD 1999b: 4ff.)

xenotransplantation. Following the presentation, the SCMPMD Chairman requested that a working party be established to identify the interesting scientific points on the subject. This working party involved six Committee members.[8] Some SCMPD members asked that external experts be integrated into the working party because its current members were not specialized in xenotransplantation. The working party was therefore asked to identify external experts and invite them to future meetings. The EMEA representative present was also invited to contribute to the work and it was agreed that the EMEA would send a document on this subject to the working party (SCMPMD 1999b).

At the 12th meeting, in December 1999, xenotransplantation was once again a topic for discussion. The working party reported on its current work and its chairman recognized that xenotransplantation had been the topic of debate at several international forums. The working party reported that it had discussed the issue and had agreed on a position paper, which would become a starting point for a more detailed document, which would be discussed by experts on xenotransplantation during a seminar that the working party had planned. Dr. Jones also stated that the work would be difficult and that a final draft was envisaged in twelve or more months (SCMPMD 1999c).

In February 2000, at the 13th meeting, Dr. Jones reported that an internal preliminarily report for the use of the working party was being prepared. The SCMPMD also decided that it should also draw the European Commission's attention to this subject. Because he was "unable to continue to chair the group" Dr. Jones suggested Dr. de Jong as a successor and asked to include yet another researcher, a veterinarian, into the working party (SCMPMD 2000a).

At the 14th meeting of the SCMPMD, in June 2000, the new Chairman, Dr. de Jong, informed the Committee about CoE documents on xenotransplantation and about his asking the Chairman of the CoE working group for cooperation (SCMPMD 2000b). The already established links between the SCMPMD and the CoE were thereby reinforced.

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[6] "non-commercialization of substances of human origin; ensure the dignity of the human being; maintenance and further realization of human rights and fundamental freedoms; protection of donors and recipients" (SCMPMD 1999b: 4).

[7] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine. No. 164 on Human Rights and Biomedicine (1997). Protocol to the Convention on human rights and biomedicine on the prohibition of cloning human beings. Protocol to the Convention on human rights and biomedicine on organ transplantation (in consult period), Recommendation No (97) on Xenotransplantation. State of the Art report on Xenotransplantation.

[8] Dr. Jones (chairman of the working party); Prof. Williams (Senior Pro-Vice-Chancellor, Dept. of Clinical Engineering, The Royal Liverpool University Hospital, Liverpool, UK), Dr. de Jong (Senior scientific staff member, National Institute of Public Health and Environment, Bilthoven, Netherlands), Dr. Silbermann, Prof. Loewer (Acting Director, Paul-Ehrlich-Institut, Langen, Germany), Prof. Descotes.

In December 2000, at the 15th SCMPMD meeting, the working group reported its plan to finalize the draft opinion by mid 2001. Also, several new members were incorporated (SCMPMD 2000c).[9]

At the 16th meeting, in February 2001, Committee members asked the working group to include several topics into the report, i.e. immunology, health of animals used in transplants, ethics, and stem cells. It was decided that the report should be discussed at the next meeting in May (SCMPMD 2001a).

In May 2001, at the 17th SCMPMD meeting, a draft report was circulated within the Scientific Committee; however, it was stated that another working group meeting would be necessary to revise and finalize the document before the next plenary SCMPMD meeting (European Commission 2001a).

The SCMPMD adopted the working groups' report "Opinion on the State of the Art Concerning Xenotransplantation" on 1st October 2001. The minutes report that, "a productive discussion on the subject took place and the members of the Committee proposed several modifications to the report and to the Opinion" (European Commission 2001b). However, the records do not provide any details of what points were discussed, what modifications were considered necessary and in what way the paper was consequently changed.

2.2 Content

2.2.1 Objective

The purpose of the "Opinion on the State of the Art Concerning Xenotransplantation" was to "report to the European Commission (DG SANCO) the current developments and concerns in the field of xenotransplantation and to indentify issues that may require community-wide action" (European Commission 2001c: 2). It should be noted, however, that the report was, as previously mentioned, solely an advice to the Commission; it did not constitute a decision on policies (see chapter 2.1.2). As a brief DG SANCO report in 2003 emphasised, the questions addressed in the Opinion on Xenotransplantation arose "on an ad hoc basis" and were "not associated with any specific legislation" (European Commission 2003: 24).

2.2.2 Framing

The SCMPMD Opinion is framed in the context of organ shortage, the risks of xenotransplantation and how to contain them, as well as a number of downstream ethical

[9] Prof. Vannier (Directeur, Laboratoire d'Études et de Recherches Avicole et Porcine, Agence Française de Sécurité Sanitaire des Aliments, Ploufragan, France), Dr. Dobbalaer (Acting Head of Biological Standardisation Section, Ministry of Public Health, Institute for Hygiene & Epidemiology, Brussel, Belgium), Prof. Williams, Dr. Thomson and Dr. Madsen (Chief Physician, Aarhus University Hospital, Department of Renal Medicine, Århus, Denmark)

considerations regarding clinical trials and animal welfare, relevant if xenotransplantation were to become a clinical reality. One interviewee described the Opinion as "focused on the public health risks" (b: 142-143), while ethical issues “were not extensively addressed. (…). The Working Group dealt more with scientific issues of xenotransplantation and potential risks, both for the patient or for the environment of the patient" (b: 317-319). As another respondent commented, the Committee focused on scientific questions and deliberately left ethical questions to politicians. The SCMPMD considered itself not as an ethics but as a scientific committee, which meant that politicians would have to take into account the ethical problems of xenotransplantation (a: 350-352).

2.2.3 Potentials, Risks and Costs

The Opinion frames xenotransplantation as an international problem and takes into account reports of international organisations such as the Council of Europe (CoE 2000), the OECD (1999), and the World Health Organization (WHO 1998; European Commission 2001c: 5, 7, 8, 10).[10]

The Opinion reports that the CoE Parliamentary Assembly unanimously adopted a recommendation to ban xenotransplantation, which called for a “legally binding moratorium on all xenotransplantation in humans, including clinical trials” (ibid. 4). The Opinion, however, states that no European wide legislation had so far implemented this CoE recommendation. The paper neither takes an explicit position against or in favour of a moratorium nor discusses the topic any further. However, it criticizes the fact that there were no information-sharing procedures in place between countries. It demands international cooperation and claims that it is necessary to “re-examine the strategies in place and options available to support and control xenotransplantation as well as to ensure public health” (ibid. 4).

Xenotransplantation, defined as transplantation of animal cells, tissues or organs into humans, is described as a promising solution to organ shortage and a possible alternative to the use of human or artificial materials.[11] Nevertheless, it is not presented as a panacea to organ shortage. On the contrary, it claims that the public should continue organ donation (ibid. 13) and that stem cell technology may be a viable alternative (ibid. 14). While organ shortage is presented as a main motive for exploring xenotransplantation, the paper does not focus on whole organ xenotransplantation. In fact, this option is dismissed as being at a

[10] This indicates an international network of scientists, experts and policy makers which already became apparent in the case of OECD xenotransplantation policies (Griessler 2012). Also Tallacchini (2011) emphasizes the cooperation between CoE and the SCMPMD. Commission staff participated, for instance, in the CoE Working Party on Xenotransplantation (Council of Europe 2003: 7) and at an international meeting organized by the OECD (Griessler 2012). Unfortunately, requests for interviews about these activities of Commission staff in xenotransplantation policies were denied.

[11] Xenotransplantation is defined as “any procedure that involves the transplantation or infusion into a human recipient of (a) living cells, tissues, or organs from a non-human animal source, or (b) human body fluids, cells, issues or organs that have ex vivo contact with living non-human animal cells, tissues or organs (e.g. extracorporal perfusion)” (European Commission 2001c: 5).

premature stage, while xenotransplantation of cells and extracorporeal liver perfusion, where clinical trials were already being carried out, is regarded as the more relevant development in xenotransplantation (ibid. 5).

The Opinion discusses the advantages and disadvantages of using non-human primates as source animals and concludes that, “pigs were the most likely species to be used in xenotransplantation” (ibid. 6).

The document identifies the possible spread of infectious diseases as the greatest problem of xenotransplantation. The significant risk that an immunosuppressed host would be infected by pathogens from transplanted animal cells would not only pose a threat to the individual patient but also to the wider public (ibid. 7). Furthermore, new diseases might arise in this manner and present new and unforeseeable health care problems of their own.

The paper discusses the management of the inherent infection risk of xenotransplantation by “breeding of pigs in a barriered environment” with regular screening for infections (ibid. 8). However, this would not help to prevent the spread of unknown viruses and PERV (porcine endogenous retroviruses), which would “pose the most obvious risk at present” (ibid. 8 ff.). Surveillance is discussed as the necessary procedure for managing what is regarded as a global infection threat posed by xenotransplantation. From this perspective, the report calls for international cooperation and suggests that an international agency such as the WHO should function as a central distributor of information. Registration, surveillance and monitoring would apply to xenotransplantation recipients as well as others at risk (such as carers, close relatives, visiting friends, neighbours and others) but would also extend to the source animals and their husbandry staff (ibid. 10).

Xenotransplantation is also perceived as a means to lowering costs in the health care system; savings may result from not having to pay for chronic treatments and by people being able to return to work (ibid. 13).

2.2.4 Ethical issues

Although the Opinion recognizes the importance of “ethical, social, and religious values and perceptions”, which might also influence the public’s perception of xenotransplantation, it does not “consider” them “in detail” (ibid. 4). Instead, it “addresses and identifies the scientific issues that are considered important areas on which the European Commission should focus” (ibid. 4). The document takes it for granted that xenotransplantation is ethically acceptable. The document intends recommendations made therein to be applied to the routine use of xenotransplantation if and when this is introduced. In other words, given that xenotransplantation were to become a routine practice, these would be the recommendations to be followed.

Ethical considerations, which are made, nevertheless arise for humans under strict surveillance conditions, which would be necessary for xenotransplantation (ibid. 10). Among the issues raised are: whom to control, for how long and whether to restrict freedom of travel. It is mentioned that some of the surveillance measures may be in violation of the Declaration of Helsinki and other guidelines for research on human subjects ("right of a subject to withdraw from a clinical trial", ibid. 11). Patients could therefore "have to agree to waive some of their human rights" (ibid.). Mariachiara Tallacchini sharply criticizes this position because it favors the prevention of collective risks over the human rights of an individual (2011: 177ff).

As already mentioned, the Opinion recognizes that "xenotransplantation raises ethical as well as scientific considerations for all those involved" (European Commission 2001c: 11). However, it does not "focus" on these questions "in detail", but instead lists a number of practical questions on such matters as "obtaining informed consent from the early clinical trial patients, the gaining of consent from non-transplanted persons in contact with the patient for surveillance purposes (including animal handling staff, nursing staff and those dealing with patient samples), archiving of samples, data protection of personal details, dissemination of results, confidentiality by contributing commercial companies, and even perhaps, how to handle breaches of agreed contract when others may be put at risk" (ibid. 11 ff.).

Members of the working party unanimously take it for granted that it is ethically permissible to kill animals in cases where there is a human health benefit. However, it is also conceded that different groups of animal welfare activists might disagree. Some of them would object to the right to kill animals altogether; others would "wish to be reassured that animals are being kept in the best possible conditions under the circumstances" (ibid. 12). It is also recognized that the breeding of transgenic animals is subject to public controversy. The report only mentions these positions without discussing them. The report deals with animal welfare issues briefly but nevertheless raises a number of practical ethical concerns and formulates several measures to address them. For example, it is mentioned that the health of source animals, i.e., should be monitored by people "trained in animal welfare assessment and the results recorded and published" (ibid.). The animal welfare problem of keeping source animals isolated in specific pathogen free or designated pathogen status is raised; due to "serious ethical concerns" it is suggested that pigs not be kept in isolators but instead in barriered groups so that they are "able to interact with other animals" (ibid. 12 ff.). This focus on practical measures might be attributable to the fact that several working party members were veterinarians by training (b: 100). However, the ethical question of trans-species transplantation, or mixing humans and non-human animals, is not discussed in the paper.

2.2.5 Public

The document does not raise the issue of public participation in the development of EU xenotransplantation policies. However, it raises the issue of public trust and calls for caution when it refers to Acquired Immune Deficiency Syndrome (AIDS) and BSE as examples of a ”public health crisis”. The Commission should be aware of “public sensitivity” in this area and take measures “to give the public confidence that the risks of xenotransplantation will be thoroughly examined” (ibid. 9).

2.2.6 Recommendations

The document includes the following recommendations (14 ff.):

I. The European Commission should propose the establishment of a centralised regulatory body to oversee the process and to minimise the risks;
II. the European Commission should carry out a thorough and ongoing risk analysis of xenotransplantation on the basis of the results of both research and clinical trials;
III. specific measures for clinical trials dealing with authorisation, informed consent, registration, surveillance of patients and those at risk should be defined on the basis of Directive 2001/20/EC of the European Parliament and of the Council “on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use” (ibid. 14);
IV. appropriate quality requirements related to health status, animal welfare and animal production should be defined and implemented for xenotransplantation source animals;
V. appropriate quality requirements for procurement of organs and their clinical use should be formulated and implemented for centres performing xenotransplantation;
VI. requirements for surveillance should be defined and implemented for source animals, xenotransplantation recipients and others at risk;
VII. the European Commission should stimulate and support research on detecting and understanding the risks of viral infections with respect to xenotransplantation;
VIII. and it should stimulate research on detecting and understanding the risks associated with severe immunosuppressive drug therapy, especially relating to interference with other drug therapy.

2.3 Policy impact

The policy impact of the Opinion is hard to substantiate for several reasons. First, as already mentioned, the initiative to deal with xenotransplantation came from the SCMPMD and was “not associated with any specific legislation” (European Commission 2003: 24). A DG SANCO report states that, “the opinions contributed to drafting of the Commission proposal

for an European Parliament (EP) and Council Directive setting standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissues and cells" (European Commission 2003: 24). However, the report does not state what these contributions were exactly. No references were made to the Opinion in available documents dealing with Directive 2001/20/EC on clinical trials. One respondent was altogether unsure what happened with the Opinion (b: 263).

2.4 Public Involvement

The main motive to create the new Scientific Committees was to regain public trust, which was severely jeopardized by the genetically modified organism (GMO) and BSE crises. The reorganisation therefore emphasised three principles, i.e., excellence, independence and transparency.

Excellence was strengthened by the objective to recruit the best scientists as well as by the central aim of the new Scientific Committees to conduct sound science without being influenced by Member States' politics. Independence was strengthened by the fact that members were no longer nominated by the Member States and had to express potential conflicts of interest. Transparency was strengthened by recruitment after open calls for expressions of interest as well as the publication of (a) selection criteria, (b) Committee members, (c) statements about potential conflicts of interest, (d) minutes, and (e) opinions.

However, although transparency was a precondition, this is not the same as public involvement. It is therefore necessary to address the question how experts and the public were involved in practices that constituted the work of the SCMPMD and which entry points for the public existed therein.

A number of routine practices can be identified in the working of the SCMPMD. These are, e.g., recruiting members, putting topics on the agenda, framing topics, recruiting working party members and external advisors, cooperating with international organisations, organising meetings, working in plenary meetings and working parties, drafting papers.

- As has already pointed out, members were not nominated by Member States but selected according to defined criteria after applicants expressed their interest in an open call. The public was informed about this process.
- The recruitment of working parties can be described as a self-selecting process of experts controlled by the SCMPMD and the Commission. Working party members were expert scientists selected from the SCMPMD members' networks, a DG SANCO pool of experts or were on the basis of a literature review.
- Topics were put on the agenda either by different DGs within the European Commission or by the SCMPMD. They either arose from the European

Commission's own needs for advice or what SCMPMD experts considered relevant developments in health. The public was not involved in this selection process.

- Xenotransplantation was framed by the SCMPMD; it was framed rather narrowly by sound science, i.e. questions which can be addressed by scientific methods. As an interviewee recalled, the SCMPMD's task was to "weigh the evidence" and to come to "a decision or conclusion" (b: 270). For the most part, ethical questions were considered to be outside of the scope of the Scientific Committee; they were restricted to animal welfare and only dealt with rather briefly. The public had no influence on how the topic was framed.
- The working party collaborated with international organisations such as the OECD. This cooperation is important because it contributed to establishing and sustaining an international network of high-level experts and policy makers (epistemic community) with shared beliefs and assumptions about xenotransplantation and its regulation (Griessler 2012).
- Plenary Meetings and even more so meetings of working parties were important occasions, where papers were drafted, discussed and rewritten. However, these documents were not open to the public. Opinions and minutes about plenary meetings were published though but, as has already been said, provided little information in terms of content. Moreover, there were no minutes of working party meetings, where most of the work was done.

The public had almost no entry points to most of the aforementioned routine practices. It was mainly defined by the SCMPMD as an outsider who should be notified about its activities with well-measured information.

3 Promising Economic Area

At the European Council in Lisbon, in March 2000, the goal to become the leading knowledge-based economy was set. The Commission therefore decided to agree on a strategy for life sciences and biotechnology for the next years.[12] The following year the Commission published the consultation document "Towards a strategic vision of life sciences and biotechnology" (EC 2001) and called for comments by interested groups and the general public. Xenotransplantation was identified as one new research area, which would potentially require further investigation. During the consultation process a stakeholder conference took place from September 27th to 28th 2001. Representatives from several DGs (Research, Health and Consumer, Enterprise and Innovation) and the Deputy Secretary General were involved. After the consultation phase, the Commission published "Life sciences and biotechnology — A strategy for Europe",[13] which consisted of policies and points of action. Xenotransplantation was described as offering the "prospect of replacement tissues and organs to treat degenerative diseases and injury resulting from strokes, Alzheimer's and Parkinson's diseases, burns and spinal-cord injuries" (EC 2002:11). It was also identified as an area where ethical considerations required further attention. The Commission monitored the implementation of its strategy and published several progress reports in 2003, 2004, and 2005, which do not refer to xenotransplantation again. Economic framing disappeared after xenotransplantation did not fulfill the Commission's high hopes.

[12] For details and reports see: http://ec.europa.eu/biotechnology/index_en.htm (accessed:1/2/12)

[13] Communication from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the Regions (COM(2002) 27), http://ec.europa.eu/biotechnology/pdf/com2002-27_en.pdf (accessed: 1/2/12)

4 Regulating Xenotransplantation

4.1 Clinical Trials

In September 1997 the European Commission sent out a proposal for a Directive regulating clinical trials[14] (Commission of the European Communities 1997), which was finally accepted more than three years later; this occurred in April 2001 after a codecision process, several amendments and compromises between the European Institutions. As Commissioner Liikanen stated in 2000 in a speech to the European Parliament, the aim of the Directive was to harmonize European legislation in order to avoid "difficulties both for participants in clinical trials and industrialists who want to conduct such trials in the European Union" (European Parliament 2000). The Directive lays down under what conditions clinical trials have to be carried out in Europe and how they are to be transformed into national law by EU Member States (Cozzi et al. 2009: 208 ff.).

4.1.1 Content

In general the Directive makes clinical trials subject to authorization by a national ethics committee and a regulatory authority (Directive 2001/20/EC: Article 2 (k), Article 6, and Article 9). In other words, approval is mandatory for each clinical trial. An authorization by a competent authority must be completed within 60 days, a period that can be extended by 30 days or more in the case of gene therapy products. The Directive explicitly addresses the use of xenogeneic cell therapy because it states that in the case of xenogeneic cell therapy "there shall be no time limit to the authorisation period" (ibid. Article 6.7). Furthermore, "written authorisation shall be required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogeneic cell therapy" (ibid. Article 9.6). Ethics committees and regulatory authorities are therefore not obliged to answer a request for a clinical trial in xenotransplantation within a certain period of time and trials cannot start until an opinion is provided. An interviewee interpreted this as a "sort of tacit, implicit moratorium or at least enabling a tacit moratorium by the Member States, because simply you can just postpone the delivery of your opinion". It is, in her opinion, "a very (…) under the surface proceeding, so keeping xeno alive and at the same time being compliant with Member States' will" (c: 231-245). The following section will address the question of how this clause came about and who was involved in its formulation.

[14] The Directive defines clinical trials as: "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and /or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy" (Directive 2001/20/EC, Article 2 (a)). As "good clinical practice" the directive defines "a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible" (Directive 2001/20/EC: Article 1, 2).

4.1.2 Procedure

Drawing on documents accessible at PreLex,[15] it becomes apparent that the law making procedure started with a proposal for a Directive (97/0197 (COD)) presented on 3 September 1997 by the Commission to the Council and the European Parliament for a codecision to be made (Commission of the European Communities 1997). The draft Directive was prepared by the Commission under the responsibility of DG03 and the involvement of six other Directorates. This draft, however, did not yet include any special clauses for xenotransplantation.

On 19 September 1997 the proposal was referred, within the European Parliament, to the Committee on Environment, Public Health and Consumer Protection as well as the Committee on Budget for its opinion. On 1 October 1997 it was also sent to the Committee on Research, Technological Development and Energy.[16] The Committee on Environment, Public Health, and Consumer Protection discussed the proposal twice in autumn 1997. Several amendments were suggested; one of which mentioned xenotransplantation:

Article 4 (4) dealt with an additional time limit for ethics committees to receive supplementary information from an applicant. Amendment 12 of Article 4 (4) of the Commission draft limited this time span to 15 days and stated that “no additional extension shall be permissible beyond that limit, except in the case of trials involving gene therapy and xenotransplantation” (European Parliament 1998a). The explanatory statement does not mention why this exception for xenotransplantation was made. The draft legislative resolution was adopted unanimously.

After its first reading on 16 November 1998, the European Parliament approved of the Commission proposal with amendments on the following day (Official Journal of the European Communities 1998: C 379/17). Amendment 12 regarding xenotransplantation was also adopted.

On 26 April 1999 the Commission adopted an amended proposal and sent it to the Council and the European Parliament on 27 April 1999. It did not take into account Amendment 12 of Article 4 (4), as requested by the European Parliament, thereby providing an exception for xenotransplantation and extending the deadline for provision of additional information to the ethics committee (Official Journal of the European Communities 1999: C 161/13).

[15] http://ec.europa.eu/prelex/detail_dossier_real.cfm?CL=de&DosId=21434, accessed 30/12/11

[16] The Committee on Research, Technological Development and Energy (Draftman Umberto Scapagnini) met three times from February to June 1998 but did not make any changes involving xenotransplantation (European Parliament 1998a).

On 25 May 2000 the Ministers' Council reached political agreement on the Directive by a qualified majority, where the Austrian delegation voted against it (Counseil/00/180).[17] The proposal was an item "B" on the Council agenda. The topic of xenotransplantation was not mentioned in the minutes. It was decided to adopt the proposal as a common position as an "A" item.

On 20 July 2000 the Ministers' Council adopted a common position as item "A" on its agenda (Official Journal of the European Communities 2000). In Article 4, paragraph 7 it states that, "No extension to the time period referred to in paragraph 5 shall be permissible except in the case of trials involving medicinal products for gene therapy and somatic cell therapy including xenogeneic cell therapy" (ibid.). Ethics committees and national authorities would therefore have unlimited time to produce an opinion in these cases. Article 7 "commencement of clinical trial" in paragraph 6 reads: "Written authorisation shall be required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogeneic cell therapy and all medicinal products containing genetically modified organisms" (ibid.). The common position is thus stricter in these cases than in other clinical trials. No clinical trials can be started without written consent, which is not bound by a time limit. The statement of reasons explains that, "The second part of amendment 12 (Article 4 (7)), concerning an exceptional extension of the 60-day period for the Ethics committee to give its opinion in cases where trials involve medicinal products for gene therapy was accepted by the Council and extended to include somatic cell therapy, including xenogeneic cell therapy" (Council of the European Union 2000: 4).

With the Rapporteur, Peter Liese, the Committee on the Environment, Public Health and Consumer Policy of the European Parliament adopted a Recommendation for Second Reading on 21 November 2000 (European Parliament 2000a). This document did not mention any amendments with regards to xenotransplantation. Xenotransplantation was also not mentioned in the parliamentary debate on 12 December 2000 (European Parliament 2000b).

On 14 December 2000 the European Council adopted a position towards the Second Reading of the European Parliament. It "approved by a qualified majority, with the Netherlands delegation voting against, all the amendments to the common position adopted by the European Parliament" (Council of the European Union 2001a: 6).[18] In another Council Meeting on 26 February 2001 a qualified majority was again in favour of the proposal, against the vote of the Netherlands.

As a result of this process at the European level there is no formal moratorium in place on clinical trials with xenotransplantation. In principle clinical trials in xenotransplantation are

[17] No explanations are given, why Austria voted in this way.
[18] No reason was given why the Netherlands voted in this way.

possible but they are subject to a regulation, which enables national authorities to postpone them for an unlimited time span. The documents accessible at PreLex show that this regulation stemmed from the European Council. However, the available documents do not provide any reasoning for why this decision was made. None of the documents provide information as to why this amendment was made and clinical trials in xenotransplantation are more restrictively regulated than in other areas.

The development of the Directive followed the process of codecision, which in a highly complex choreography involves different players in the European Commission, the European Council and the European Parliament (Pernicka/Biegelbauer 2002, Peterson/Bomberg 2000, Wallace 2005). This process remained highly opaque to outsiders and the public because there was only little information available to explain why certain decisions were made and where the impetus to make them came from. Interested citizens can get information by visiting the official PreLex website and downloading the published documents but these sources do not provide an answer to the question of why these particular policies were made. They lack any explanatory information about this issue. This state of opaqueness is aggravated by the fact that it turned out to be impossible to get more information about the law making process because an interview with the responsible Rapporteur was denied. It remains unclear whether the SCMPMD Opinion was taken into consideration at all, and which experts and stakeholders were involved as advisors on what issues. The complexity and insulation of this law making process and the scarceness of information available is one important factor hampering citizen participation in European Institutions.

4.2 Medicinal Products

At the EU level several legally binding provisions for xenotransplantation exist. These include Directive 2001/83 EC on the Community code relating to medicinal products for human use (amended by Directive 2008/29/EC), the already discussed Directive 2001/20/EC on clinical trials and Regulation (EC) No. 726/2004 that lays down Community procedures of the supervision of medicinal products for human and veterinary use and establishes a European Medicines Agency (Straßburger 2008: 299).[19] We will only briefly deal with these Directives and Regulations because the process of their development and involvement of the public do not differ to a great extent from the process already described. Instead we will look more thoroughly into the way in which the European Medicines Agency produced its guidelines.

4.2.1 Directive 2001/83/EC

In 2001 Directive 2001/83/EC, on the community code relating to medicinal products for human use, was established (Cozzi et al. 2009: 208). There were no specific provisions on

[19] In 2001 Directive 2001/18/EC, on the deliberative release into the environment of genetically modified organisms, established legal provisions applicable to xenotransplantation although this was not directly addressed (Cozzi et al. 2009).

using xenogeneic cells. In 2003 this Directive was amended by Commission Directive 2003/63/EC. Regulatory oversight on xenotransplantation, in the field of medicinal products, was thereby established since xenogeneic cell therapy was incorporated into the Annex I (Part IV) to the EU Directive on medicinal products. Part IV.4. A "specific statement on xeno-transplantation medicinal products" states that, "detailed information related to the following items shall be provided according to specific guidelines:

- Sourcing of the animals
- Animal husbandry and care
- Genetically modified animals (methods of creation, characterization of transgenic cells, nature of the inserted or excised (knock out) gene)
- Measures to prevent and monitor infections in the source/donor animals
- Testing for infectious agents
- Facilities
- Control of starting and raw materials
- Traceability (Directive 2001/83/EC)

4.2.2 Regulation (EC) No 1394/2007

In December 2007 Regulation (EC) No 1394/2007 on advanced therapy medicinal products (ATMP) was approved and actually entered into force on 20 December 1998. ATMP include products relating to gene therapy, somatic cell therapy and tissue engineering (Cozzi et al. 2009: 209).[20] The main goal of the Regulation was to establish "a centralized authorization procedure for all AMTP through an interdisciplinary expert committee, the Committee for Advanced Therapies (CAT) within the European Medicines Agency (EMA), as the main accountable body in defining and evaluating advanced therapies" (Tallacchini/Beloucif 2009: 184). This also included "specific provisions concerning the authorisation, supervision, and pharmacovigiliance of xenogeneic medicinal products" (Straßburger 2008: 299, Tallacchini/Beloucif 2009: 183). Once granted by the European Commission, a centralised marketing authorization is valid in all European Union and EEA-EFTA[21] states. The main responsibility of the CAT is to prepare a draft opinion on each ATMP application submitted to the European Medicines Agency, before the EMEA's Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion on the granting, variation, suspension or revocation of a marketing authorisation for the particular medicinal product.

During the inter-institutional negotiations over the ATMP regulation, ethical concerns generated political conflict. Some stakeholders raised objections to the use of human embryonic stem cells, or human-animal hybrids. The regulation therefore states that it does

[20] Up to 2008 regulations for cell-based therapies and tissue-engineering products were developed separately from those concerning xenotransplants, but Regulation (EC) 1394/2007 meant that the European Union had one single regulatory provision covering all ATMP (human and animal).
[21] Iceland, Liechtenstein and Norway

not override member states' individual decisions on the use of specific human (e.g. human embryonic stem cells) or animal cells (Farrell 2009: 55).

4.2.3 Guidelines Developed by EMA

The Commission set up various decentralized agencies to cope with the exceedingly demanding EU regulation. One of these, the European Medicine Agency (EMA) deals with the "evaluation and supervision of medicines for human and veterinary use" in the EU (European Medicines Agency 2012, Garattini/Bertele 2004). Though EMA has no formal power to make decisions concerning the authorization of medicinal products, it is "*de facto*, if not *de jure*, a 'quasi'-decision-making agency as the Commission normally decides upon its recommendations" (Borrás et al. 2007: 592, emphasis in the original).

As already mentioned, Regulation (EC) 1394/2007 established a centralized market authorization procedure. Medicines that must be approved by the EMA through this procedure include: all medicines for human and animal use derived from biotechnology and other high-tech processes, all advanced-therapy medicines and human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, all designated orphan medicines intended for the treatment of rare diseases, as well as all veterinary medicines intended for use as performance enhancers. Other tasks of the EMA include monitoring the safety of medicines through a pharmacovigilance network, playing a role in stimulating innovation and research in the pharmaceutical sector and providing scientific advice and other assistance to companies for the development of new medicines. The EMA also publishes guidelines on quality, safety- and efficacy-testing requirements.

4.2.3.1 Organization

A 35-member management board, whose members should be independent from any government or organisation, sets the Agency's budget, approves the annual work programme and is responsible for ensuring that the EMA works effectively and cooperates successfully with partner organisations across the EU and beyond. EMA staff is responsible for the administrative and procedural aspects of European Union regulations and directives related to the evaluation and safety-monitoring of medicines in the EU. The Agency's six scientific committees[22] are composed of independent professionals nominated by Member States from a pool of over 4,500 European experts. These committees are responsible for the scientific evaluation of marketing authorisation application dossiers submitted by pharmaceutical companies. They also provide opinions on referrals and other issues

[22] These are: Committee for Medicinal Products for Human Use (CHMP), Committee for Medicinal Products for Veterinary Use (CVMP), Committee for Orphan Medicinal Products (COMP), Committee on Herbal Medicinal Products (HMPC), Paediatric Committee (PDCO), Committee for Advanced Therapies (CAT)

impacting on public health, at the request of the Member States, the European Commission or the European Parliament.

The Committee for Medicinal Products for Human Use (CHMP) is responsible for preparing the EMA's opinions on all questions concerning medicinal products for human use, including xenogeneic cell therapy medicinal products, based on a draft opinion for ATPM prepared by the Committee for Advanced Therapies (CAT). The CHMP also provides scientific and regulatory guidelines for the pharmaceutical industry, e.g. the "Guideline on Xenogeneic Cell-Based Medicinal Products" (European Medicines Agency 2009).

CHMP members and alternates are nominated by the Member States, in consultation with the European Medicines Agency Management Board. They serve on the committee for a renewable period of three years.[23] The CHMP has several working parties and scientific advisory committees. Within the CHMP there are also temporary working parties, drafting groups, scientific advisory groups and other CHMP-associated groups.[24]

The CAT's (Committee's for Advanced Therapies) main responsibility is to assess the quality, safety and efficacy of ATMPs and to follow scientific developments in the field. It is a multidisciplinary committee, also including two representatives from patient organizations.

4.2.3.2 Development

Already in 2000 the Biotechnology Working Party in the Committee for Proprietary Medicinal Products (CPMP)[25] suggested that a guidance document on xenogeneic cell therapy products be produced (EMEA 2000). The impetuses for such a document were perceived regulatory gaps and the fact that manufacturers were already "developing xenogeneic cell therapy products" (ibid. 1). The paper proposing such a document also pointed out that, "the use of xenogeneic cells or tissues involves serious ethical, scientific, public health and other issues" (ibid.). However, it also clarified that the planned guidance document did "not indicate an acceptance of clinical development of xenogeneic cell products, but rather, should serve as a tool for harmonising the approach to the evaluation of medicinal products containing xenogeneic cells" (ibid.). The aim of a guidance document was "to establish a common scientific view with the European Union on the special requirements concerning quality,

[23] The CHMP is composed of:
- a chairman, elected by serving CHMP members;
- one member (and an alternate) nominated by each of the 27 EU Member States;
- one member (and an alternate) nominated by each of the EEA-EFTA states, Iceland and Norway;
- up to five co-opted members, chosen among experts nominated by Member States or the European Medicines Agency and recruited, when necessary, to gain additional expertise in a particular scientific area.

[24] The current CHMP standing working parties are: Biologicals Working Party, Patients' and Consumers' Working Party, Pharmacovigilance Working Party, Quality Working Party, Safety Working Party, Scientific Advice Working Party.

[25] The CPMP is the predecessor of the already mentioned CHMP.

safety, efficacy and surveillance of xenogeneic cell therapy medicinal products. It is a means for harmonization of the technical requirements" (j: 3). The planned guidance document was to cover the issues of "choice of animal species, animal husbandry, quality issues in the production process, requirements for preclinical testing, requirements for clinical evaluation, need for special clinical safety monitoring (…) public health issues" such as "follow up of individuals in close contact with the patient, archives for human tissue samples, need for special surveillance systems" (EMEA 2000: 2). The document proposed the creation of a multidisciplinary team, including veterinary experts, for the organization of expert meetings on the topic.

Since the development of the guideline was a multidisciplinary task, the group responsible for drafting the document "included members ('Rapporteurs') from the Biotechnology Working Party, the Safety Working Party, the Efficacy Working Party and the Pharmacovigilance Working Party, together with veterinary experts in the field of animal husbandry, viral risk and zoonoses. EMA staff assisted this expert group" (j: 2).

In 2001 the ad hoc group on xenogeneic cell therapy met twice and prepared a "points to consider document on the quality and manufacturing aspects of cell therapy products" (EMEA 2002a: 20). A further meeting was held in February 2002, during which the experts "reviewed current scientific and regulatory approaches and experience in this field". The meeting focused on "safety aspects, methods available to minimize viral risks, special methodological aspects to be considered for clinical efficacy, post exposure safety monitoring and surveillance" (CPMP 2002a: 20). In 2002 an expert workshop was held, which involved "experts in the field, members from the involved working parties, representatives from US-FDA[26] and US-CDC[27] representatives from the European Commission and the Council of Europe" (j: 2). In addition, a Rapporteur's meeting was held in the same year, which should have "allow(ed) the Rapporteurs from the different working parties to gather the latest scientific information" and "to finalize the draft xeno guidance" (j: 3). These two events "led to the preparation - in consultation with the reworking parties and the CVMP - to a Points to consider paper on xenogeneic cell therapy medicinal products" (EMEA 2002b: 23).[28] The paper was released for a six months' consultation period in November 2002 (CPMP 2002b: 23).

The final 24-page version of the "Points to Consider on Xenogeneic Cell Therapy Medicinal Products" was published in December 2003 (EMEA 2003). Again, it explicitly stated that it would not discuss religious, ethical or legal implications of xenotransplantation, as this was not the Committee's task (ibid. 3). It emphasized that the guidelines should not be interpreted as a promotion of clinical trials, including animal cells (ibid.). Rather, they were intended to provide some general principles that could be used if regulatory agencies within

[26] Food and Drug Administration
[27] Center for Disease Control and Prevention
[28] CVMP = Committee for Medicinal Products for Veterinary Use.

the EU were to deal with a marketing authorization application. In the document, xenogeneic cell therapy[29] is regarded as attractive due to the limited availability of human cells and the relatively reduced risk of immune rejection compared with solid organ xenograft (ibid. 16). It formulates a complex and wide ranging system of regulations including documentation, long term archiving and surveillance, which must be in place before products using xenogeneic cells were authorized to enter into preclinical and clinical testing. The document covers the following issues in detail:

- Sourcing of animals
- Manufacturing
- Non-clinical testing
- Human efficacy and safety
- Pharmacovigilance and special surveillance methods

In October 2009 the CHMP adopted the "Guideline on Xenogeneic Cell-Based Medicinal Products". This much shorter 14-page document replaced and revised the 2003 "Points to Consider". The purpose of these guidelines was to provide general principles for the development and assessment of xenogeneic cell-based products to ensure that these are of acceptable quality and standard as well as free of contamination. While intended for products entering the marketing authorization procedure, the document emphasises that guidelines should already be considered at the earlier stage of entering into clinical trials. The document focuses on scientific requirements but also identifies requirements for suitable animal husbandry, in terms of animal welfare, thereby also including ethical considerations (European Medicines Agency 2009).

The Cell Products Working Party (CPWP), in cooperation with other relevant working parties, prepared the first draft of the guidelines. The EMA stated that, "CAT and CHMP members were involved in the preparation of the draft guideline through regular updates and the opportunity for comments at all milestones (e.g. draft to be released for public consultation). This guideline was presented to the CAT and CHMP for comments and adoption. The CAT and CHMP adopted the final version on 22 October 2009" (j).

4.2.3.3 Framing

The immediate exclusion of the religious and ethical implications of xenotransplantation runs like a red thread through all published EMEA/EMA guidance documents. The topic of xenogeneic cell transplantation, though it has, e.g. serious legal implications concerning informed consent and surveillance, is only discussed in the context of sound science, i.e.

[29] Xenogeneic cell therapy was defined in the document as "the use of viable animal somatic cell preparations suitably adapted for: (a) the transplantation/ implantation/ infusion into a human recipient or (b) extracorporeal treatment through bringing (non-human) animal cells into contact with human body fluids, tissues or organs" (EMEA 2003: 3).

"proven quality, safety and efficacy“ (j: 3). Therefore, as EMA states: “Any guidance developed by the scientific committees of the EMA will therefore not address ethical or religious considerations, which are outside the remit of the EMA and which are the responsibility of the individual member states” (ibid.).

4.2.3.4 Consultation

Farrell (2009: 55) characterizes the regulation of cells and tissues within the EMA as “a largely technocratic-driven process (…) mediated by those with scientific expertise”. However, Regulation 1394/2007 also lays down two rules which could transcend a narrow technocratic decision making process:

- The CAT is not only composed of members with a scientific background but also includes members representing patient organisations. In addition, it should include ethicists.[30]
- Moreover, Regulation 1394/2007 established stakeholder involvement by declaring that, “open consultations with all interested parties, in particular member state authorities and the industry, have been carried out in order to capitalize on the limited expertise available in this area, and to ensure proportionality” (Regulation 1394/2007: (21)).

All scientific EMA guidelines are published on the EMA website as draft guidelines for public consultation. Both the 2003 as well as the 2009 document were open for public consultation, from November till May 2003 and February till August 2009, respectively. However, the documents do not provide any information on the result of the public consultations and in what way they were taken into consideration.

Emanuele Cozzi et al. criticized the 2009 guidance document for failing “to address several important issues. These include the responsibility for conducting the xenotransplantation study according to the highest GCP[31] standards, the definition of the long-term clinical surveillance of patients and their close contacts, sample archiving, the non-exclusion of paediatric subjects, and the absence of reference to xenotourism” (Cozzi et al. 2009: 209). The International Xenotransplantation Association commented on the EMA paper (d: 217-220) but it is not clear how or whether this was taken into account because, on request, the

[30] “The Committee for Advanced therapies should gather the best available expertise on advanced therapy medicinal products in the Community. The composition of the Committee for Advanced Therapies should ensure appropriate coverage of the scientific areas relevant for advanced therapies, including gene therapy, cell therapy, tissue engineering, medical devices, pharmacovigiliance and ethics. Patient associations and clinicians with scientific experience of advanced therapy medicinal products should also be represented” (Regulation 1394/2007: (11))

[31] Good Clinical Practice

EMA stated that it received comments from three stakeholders in 2009 (j), the International Xenotransplantation Association not being among them.[32]

Susana Borrás et. al. (2007: 593) described the systematic coordination of scientific inputs from different stakeholders of the EMEA's decision as scarce and claimed that "information asymmetries in favour of industrial actors" were present in "highly technical regulatory areas, such as pharmaceuticals", which would disfavour "groups that lack necessary cognitive resources to influence the policy process effectively". Public participation would therefore be inadequate because the "authorization process comprises several formal and informal interactions between the agency and industry that are insulated from the public and other stakeholders" (ibid.).

In summary, the procedures at the EMA are framed by sound science; ethical, legal and social aspects are deliberately excluded. The EMA does not carry out a discussion on such fundamental questions. On the contrary, the questions addressed are intended to give guidance to applicants for medicinal products and so very much downstream oriented. Although the guidance document emphasizes that it does not set a precedent for allowing clinical trials and authorizing products, it is nevertheless an important prerequisite for realizing xenotransplantation. The discussions on the guidance documents involved in-house experts and selected additional experts, as well as experts from other international organizations and the U.S. There was the opportunity for public consultations. However, within the research field of xenotransplantation, it is disputed whether all comments have been taken into account. Consultations were mainly used by expert and regulatory organisations.

[32] These were: Medicines and Healthcare products Regulatory Agency (MHRA), the Paul-Ehrlich-Institute (PEI) and the Institute National de la Santé et de la Recherche Médicale.

5 Non-human Primates in Research

5.1 Background

A topic that has been widely discussed in relation to xenotransplantation is animal welfare and animal rights. It became relevant in the EU in the regulation of the use of non-human primates (NHP) for experimentation. Pig islet xenotransplantation is currently the most promising form of xenotransplantation but is still at a preclinical stage (Dominic 2005; Dufrane et al. 2006; Dufrane/Gianello 2008; Cozzi 2008). Adult porcine islets provide a source of insulin-producing cells and could be used in treating diabetes. For ethical and safe clinical trials to commence, more preclinical data is required. The pig-to-primate model is a necessary requirement for pig-to-human transplantation of islets to become a possibility. Nonhuman primates are also used as models in research on immunosuppression.

5.2 Basic Process and Content

On 25 September 2007, the European Parliament adopted a declaration urging the Commission and the Council of Ministers to end the use of apes and wild-caught monkeys and to establish a timeline to replace all non-human primates in scientific experiments (European Parliament 2007a, 2007b, Tallacchini/Beloucif 2009). The same year a group of European citizens sent a formal petition to EU Institutions, asking that experimentation on nonhuman primates be stopped (Tallacchini/Beloucif 2009).

On 6 May 2008, the European Commission Environment Directorate General (DG ENV) responded by asking the Scientific Committee on Health and Environmental Risks (SCHER) to produce an opinion “on the possibilities to replace the use of non-human primates” in research (European Commission 2008a). The opinion should cover:

1. areas of research and testing of products and devices, in which NHP are used today;
2. currently available possibilities to replace their use;
3. an outlook on replacement in the short, medium and long term by type of research and area of testing;
4. opportunities for the reduction and refinement of their use, where no replacement seems possible in the medium term;
5. the “Research areas which should be promoted to advance replacement, reduction and refinement of the use of non-human primates in scientific procedures” (SCHER 2008c);
6. implications for biomedical research in case of a ban on the use of NHP in the EU (c.f. ibid.).

Since this opinion, unlike the 2003 SCMPMD opinion (see chapter 2.1), was associated with current legislative activity, namely the revision of Directive 86/609/EEC, there was considerable time pressure to draft an opinion. The minutes state that the "scientific opinion would need to be available by the end of October 2008 to support the codecision procedures and the related discussions at the European Parliament and the Council" (European Commission 2008a: 3)

The topic of NHP was on the SCHER's agenda in five plenary and several working group meetings from May 2008 until January 2009.

Following the rules of procedures for Scientific Committees, defined by the European Commission (2004: Article 7), the SCHER established a working group to draft its opinion. This group, comprising of Committee members and external experts, was recruited in a self-selecting process.[33] According to the rules of procedures, at least one working group member had to also be a Committee member. This person was also to hold the position of chair and was in charge of designating external members in consultation with the Scientific Committee (European Commission 2004: 7.2; 7.3). Recruitment of external experts was done in a dialogue between the DG SANCO, the Scientific Committees and the experts already identified (e: 66-70, 108-110). The working group contacted possible external experts and finally, as stated in the SCHER minutes, was able to cover "all the fields of expertise needed for the preparation of the opinion" (European Commission 2008c: 3). Throughout its existence, the working party met five to six times to draft the opinion (e: 154). On 13 January 2009, the SCHER finally adopted the paper (SCHER 2009).

The SCHER strictly restricted its scope of analysis – in the same way as the SCMPMD and the EMA - to scientific questions, explicitly leaving out ethical, legal and social aspects of the use of NHP. The Opinion stated that, "the mandate for SCHER specifically excludes ethical, economic, cultural and social aspects of NHP use as this is dealt with by other groups within the EU Commission and the EU Parliament" (SCHER 2009: 7). The SCHER concluded that from a scientific point of view "developing and testing xenotransplantation methodologies" was one of four areas, in which "the use of NHPs, at the present time, is essential for scientific progress" (ibid. 21). It recognized that artificial organs, tissue engineering and stem cells might be alternatives to xenotransplantation but dismissed these alternatives for the time being because artificial organs would be "no alternative to organ transplantation" and "complex functions of organs such as the liver cannot yet be replicated" (ibid. 25). Stem cell and tissue engineering were regarded as "still in an early research stage and far away from

[33] The final working group members included from SCHER Prof. W. Dekant (Chairman and Rapporteur), University of Würzburg and Dr. E. Testai, Instituto Superiore Sanità. External experts were: Dr. C. Bernardi, Preclinical Compliance Unit, Nervian Medical Sciences, Prof. C. Cavada, University of Madrid, Dr. D. Jones, EMEA Safety Working Party, Prof. D. Morton, University of Birmingham, Dr. E. Procyk, Stem Cell & Brain Research Institute, Prof. M. Spangberg, Swedish Institute for Infectious Diseases Control, Dr. C. Stark, Systemic and Reproduction Toxicology Unit, Bayer, Dr. J.W. van der Laan, EMEA Safety Working Party, Dr. K. Wickstrom, Medical Products Agency.

clinical applications" (ibid. 27). NHPs would therefore further be needed in xenotransplantation. Xenotransplantation was not the main focus of the paper but a "subordinated border area" (e: 135), which was brought into the working group by an external member (e: 100-101)

5.3 Impact

Already before the SCHER adopted the Opinion, the Commission published a proposal to revise Directive 86/609/EEC on 5 November 2008 (EC 2008). The aim of this proposal was to strengthen the protection of animals used in scientific experiments and to ensure their welfare. It also intended to ensure fair competition for industry and boost research activities in the European Union. In this proposal, the European Commission already determined that an outright ban on the use of animals in research was not possible. This statement was backed by an Opinion by the Commission's Scientific Steering Committee published in 2002, which stated that NHP were needed in biomedical research. On 8 September 2010, the European Parliament adopted the new Directive, in agreement with the Council, to revise Directive 86/609/EEC on the protection of animals used for scientific purposes (Directive 2010/63/EU). It acknowledged that animals, including NHP, were still needed for scientific research.

5.4 Public Involvement

In 2007, Pilot Dialogue Procedures introduced instruments for the incorporation of stakeholder input into scientific opinions (EC 2007). The aim was to "find the most effective means to interact with (…) stakeholders in an even handed and open way" (ibid. 1). The procedures specified in this Commission paper demonstrate the key challenges of stakeholder involvement in scientific committees as already pointed out in the previous chapters of this report: while public involvement is deemed necessary to implement the principles of "transparency, (…) openness and accountability", the very involvement of stakeholders is considered as a threat to the routines of scientific committees.

Firstly, stakeholder involvement exposes committees to public scrutiny, influence and even pressure. The Pilot Dialogue Procedures therefore emphasise that the independence of the scientific committee from "any influences" must be retained (ibid.). Stakeholders "must not (…) interfere with the internal work of the Committees, claiming a right or trying to be involved in such work or exerting pressures on Committee members" (ibid. 1ff.). Secondly, public involvement might change the framing of problems. However, the focus on scientific questions and sound science must be preserved. The objective of stakeholder consultations is therefore to "gather specific comments and suggestions *on the scientific basis of the opinion, as well as any other relevant scientific information* regarding the questions addressed, in order to allow the Scientific Committees to focus on issues which need to be further analysed" (ibid. 8, emphasis added). In order to be able to put forward their

comments, stakeholders therefore have to follow strict requirements regarding format and content, otherwise their comments are dismissed. A further factor restricting stakeholder involvement, as defined in the Pilot Dialogue Procedures, is that involvement does not necessarily mean dialogue and accountability. The Scientific Committee does not respond to the comments (ibid. 9). Furthermore, no reports are foreseen to document consultation processes for stakeholders (ibid.).

Stakeholders can be involved at different stages of a scientific opinion. They can:

- suggest new topics, which the Commission may consider to submit to a Scientific Committee,
- contribute to the finalisation of new mandates,
- respond to calls for data and information and/or provide scientific input during the preparation of the Opinion,
- participate in public consultations on preliminary reports, and/or
- submit scientific comments on existing opinions (c.f. ibid. 2).

During the drafting of the Opinion on NHP, a public consultation on the working mandate and a public hearing were carried out to involve the public.

5.4.1 Public Consultation on the Working Mandate

According to the European Commission, "the Scientific Committee may decide to submit its opinion to a public consultation where the Committee and Commission decide that it would enhance the quality of the work. In this case, a preliminary opinion, allowing comments from interested parties and other stakeholders, within a set deadline, will be published on the Commission's website. The Scientific Committee will take account of the comments received when adopting its final opinion" (European Commission 2004: 23.c.).

The minutes of the SCHER's 23rd plenary meeting mentioned that a public hearing on the working mandate was envisaged to take place from 15 May to 6 June 2008. On the SCHER's website, the European Commission published a "Call for information" for a "Public Consultation on 'working mandate' and call for the submission of information or data on the need for non-human primates in biomedical research, production and testing of products and devices" (SCHER 2008a, emphasis in the original). The call included a link to the working mandate (SCHER 2008c), the Pilot Dialogue Procedures (EC 2007a) and Guidelines for Submissions (N.N.: w. d. a). It provided information on the DG ENV's request for an Opinion and invited interested parties to submit scientific contributions by 6 June 2008 (SCHER 2008a). These contributions included:

1) "Scientific peer reviewed research papers, reviews and reports (later than 1990) on test, methodology and possible alternatives related to the use of non-human primates in biomedical research, production and testing of products and devices
2) Other credible scientific information that may not be easily available and which is directly relevant to this issue" (SCHER 2008a).

Thus the call made it very clear that the contributions should only cover "credible scientific information". Whether the SCHER took contributions into consideration depended on several strict criteria:

1. "it is directly referring to the content of the report and relating to the issues that the report addresses,
2. it contains specific comments and suggestions on the scientific basis of the opinion,
3. it refers to peer-reviewed literature published in English, the working language of SCHER and the working group,
4. it has the potential to add to the mandate and the opinion of SCHER" (SCHER 2009: 37).

The minutes of the SCHER's 24th plenary meeting, held in Brussels on 15 July 2008, gave a very brief account on the public consultation, revealing only that the consultation was held and that "around 700 scientific articles and 140 comments were received".[34] It was mentioned that the working group would review these contributions. The consultation also had actual implications for the working group, since the records state that more external experts would be needed "to cover some points of the request" (European Commission 2008b).

5.4.2 Public Hearing

At SCHER's 24th Plenary Meeting, the working group and the Commission recognized that the opinion had to be prepared within a "tight deadline" and decided not to "proceed with a public consultation on this very sensitive issue" but instead "organize at least a public hearing on the use of non human primates in research" in November 2008 (SCHER 2008b: 3ff.).

This public hearing, at which the draft opinion was subject to discussion, took place on 6 November 2008. To be eligible for participation, interested stakeholders were required to be scientists or technical experts with expertise in the field and to identify a particular subject matter they wished to address with appropriate scientific evidence relevant to the subject (SCHER 2008b). The call for participation states that, "when submitting their application,

[34] The Opinion gives the exact numbers with 628 scientific articles and 84 comments received "from non governmental organizations, industry, academia, public authorities and individuals" (SCHER 2009).

potential participants should provide full professional details, specify the particular topic they wish to address in the hearing giving technical justification for their request" (ibid.). Also, the number of participants was limited to "two representatives for each registered organization" (ibid.) due to space restrictions. The Commission services and the SCHER selected participants according to certain criteria:

- "Based on the technical justification provided, the participant is expected to provide scientific evidence with a relevance to the subject;
- Interested participants have clearly identified the subject matter they would wish to address and have provided sufficient technical justification;
- Interested participants are scientists or technical experts with an appropriate expertise in the field who are able to appropriately present and understand the scientific arguments" (SCHER 2008b).

In the meeting itself, 48 representatives of various stakeholders including academia, NGOs, industry, and governmental institutions participated (N.N.: w. d. b). There was little information available about the meeting except a short, 5-line report, which only stated that "the outcome of the discussion together with material submitted subsequently, were considered in the final opinion" (ibid. see also SCHER 2009: 37).

As a consequence of the hearing, two working group meetings were planned to enable the working group "to go through to the contributions received by stakeholder participating in the hearing" (European Commission 2008d). The final Opinion stated that, "each submission which met (the) criteria has been carefully considered by the Working Group. The scientific rationale of the opinion has been revised to take into account relevant comments and the literature has been updated with relevant publications" (SCHER 2009).

Nevertheless, an animal rights' NGO, the European Coalition on the End of Animal Experiments (ECEAE), who, according to their Website, participated in both the consultation and the hearing, contested the Opinion (ECEAE 2009). They forwarded a complaint with the Ombudsman of the EU claiming that the working group did not have enough expertise in the area of NHP research and did not take into account the latest scientific evidence and statements made by interest groups on alternatives to NHP research. The ECEAE challenged the Opinion with scientific arguments, contesting the Committee's adequacy and the completeness of the scientific evidence considered (ibid.).

5.5 Summary

During the course of approximately a decade, the European Commission introduced a number of measures to increase transparency, independence and excellence of its scientific committees.

- In principle, stakeholders can suggest new topics, "which the Commission may consider to submit to a Scientific Committee" (European Commission 2004: 2). This was not the case in the Opinion on NHP; the topic was raised by the European Parliament and by petitions of European citizens (European Commission 2007).
- Several documents were made available on the Internet (European Commission 2004: 5.3.). Inter alia the minutes of plenary minutes are published. They included a list of participants, declarations of interest, adopted agenda "summary of discussion, including important minority stand points and agreed actions", "a record of decisions taken and opinions adopted" and abstentions during voting (European Commission 2004: 21).
- Moreover, active stakeholder involvement is organized; during a consultation phase and public hearing, NGOs were able to comment on the working mandate and the draft opinion.
- NGOs were able to send a complaint to the European Ombudsman.

However certain factors limited transparency and openness:

- Requests for an Opinion have to come from the Commission (European Commission 2004: 13). The Scientific Committee can raise issues and it is up to the Commission to decide which action to take including "a request for a scientific opinion or a report on the matter" (ibid. 16.2).
- Recruitment of a working party is clearly a self-selecting process (e: 286, "the group co-opts itself") (c.f. also European Commission 2004: 7). Access to committees is restricted to scientists. However, as a consequence of the public consultation, more experts were needed.
- The work of the Scientific Committee was strictly framed and confined by sound science. ELSA aspects were explicitly excluded. Participants who wanted to contribute to the debate had to follow this framing and were otherwise denied access.
- The discussion within plenary and working group meetings is not public and committee members are bound by confidentiality. The rules of procedure determine that "individual views, whether expressed orally or in writing by members, associated members and external experts during deliberations within the Scientific Committee or a Working Group shall be confidential" (European Commission 2004: 12.3.).
- In order to be accepted as participants in a public hearing and consultation, strict requirements had to be met in terms of format and content of contributions. Moreover, the number of participants was restricted.
- Although the SCHER claimed that stakeholder comments contributed to the Opinion, it is completely unclear in what way and to what extent this happened, since the scientific commission is not obliged to reveal this information.

6 Funding Research

The EU was not only active in regulating but since 1997 also in funding xenotransplantation research. In total, thirteen projects were identified that received funding in the Fifth, Sixth and Seventh Framework Programmes (see Table 2 to 5). Most of the projects were genuine xenotransplantation research but several of them dealt with xenotransplantation from an ELSA perspective. Many projects were rather small individual fellowship grants but there was also a series of financially more substantial, integrated projects, such as:

- "Xenotransplantation – strategies for the prevention of carbohydrate related (hyperacute) rejection"[35]
- "Pathogenesis, epidemiology, immunopathology, and diagnosis of post-weaning multisystemic wasting syndrome (PWMS): an emerging disease of swine due to new porcine circovirus (PCV2). Development of recombinant vaccines"
- "Engineering of the porcine genome for xeno studies in primates: a step towards clinical application (XENOME)"

The Commission's general rationale for funding health related research is to improve both the health of Europeans as well as the economic position of Europe; it was described by an interviewee as intended "to improve quality of life and health of the citizens and to improve the competitiveness of the European industry" (g: 257-258). Xenotransplantation was funded under the heading of "new therapies" (g: 16), which includes "non-pharmaceutical cell based therapies, tissue engineering, gene therapy, regenerative medicine (...) human embryonic stem cells, stem cells" (ibid. 17-19). Public funding in this area is considered justified if several conditions are met; these include cases where new therapies (a) would have a high potential to cure life threatening, currently incurable diseases; (b) they would be at a very early stage of development, and, (c) although they would be risky there would be "proof of principle", mostly in animal models, that research therein was "worth trying" (c.f. g: 16-26). Within the "wider program" of new therapies, xenotransplantation was described by an interviewee as one of several "routes" to alleviate organ shortage, amongst treatment of diseases leading to organ failure, regenerative medicine, and artificial organs (g: 36-41; 48-56; 99-102). After a "hiatus" (g: 64) of funding, stimulated by a concern about porcine endogenous retroviruses (PERV) and potential cross-species infection, in 2006 the European Commission started funding the integrated project XENOME, which looks at solid organ and cellular xenotransplantation. The fact that the risk of cross infection was no longer regarded as an issue necessarily blocking research encouraged this renewed interest. (g: 68-70). XENOME is "the principle European effort in the field of xenotransplantation" (Stein 2010: 13). Commissioner Geoghegan-Quiinn referred to the project as "the reference for

[35] For a detailed description of this research project, which also involved researchers from the social sciences and humanities to address ELSA of xenotransplantation see the Case Study on Sweden within the CIT-PART project (Hansson/Lundin 2011).

European efforts in xenotransplantation research, with islet and neural cells representing the areas with greatest potential to take towards the clinics" (E-9429/2010).[36]

The European Commission also funded a number of projects, which dealt with ELSA of xenotransplantation:

- The project "Xenotransplantation: ethical, social, economical and legal aspects" provided an overview on ELSA in this area as well as on international regulation (Jansen/Simon 2008a, 2008b, 2008c, 2008d, 2010).
- The project "Increasing Public Involvement in Debates on Ethical Questions of Xenotransplantation (XENO)" aimed at improving stakeholder debates in ELSA of xenotransplantation (Griessler/Littig 2003, 2006). Evaluators recommended this project because they considered xenotransplantation as "a growing issue" in which "more and more public concern about the use of (…) animal-parts in medical treatment"(h: 44-46) could occur.
- DECIDE, a project in which laypeople are informed in a game setting about and discuss diverse controversial technologies, also includes xenotransplantation as a topic.[37]
- CIT-PART, of which this report is part of, can also be considered as an ELSA project in this area.

These projects received funding under the "Science and Society" Programme but with two exceptions, as it was renamed "Science in Society". Their funding is based on a model of citizen participation that departs from that of the scientific advisory system, described in earlier chapters. Drawing on GMO as a text book case for a technology which caused public resistance and political crisis, these programmes, in order to avoid such intractable confrontation, emphasise early engagement with the public, participatory technology assessment (h: 12-14)[38], mobilization and mutual learning actions[39] (h: 79-80) as well as responsible research and innovation.

An interviewee perceived the GMO case as an example of a technology in which scientists and policy makers did not take into account that "public opinion might not like a technologically attractive solution" (h: 74). This attitude caused "huge problems with protests

[36] XENOME addressed in one work package also ELSA http://www.xenome.eu/ (accessed: 24/1/2012).

[37] www.playdecide.eu/play/topics/xenotransplantation (accessed: 27/1/2012).

[38] An example for several projects funded by the European Commission in this area is the current PACITA project. www.pacitaproject.eu/?page_id=506 (accessed: 1/2/12); another one the Meeting of Minds - European Citizens' Deliberation on Brain Science, http://www.meetingmindseurope.org/europe_default_site.aspx?SGREF=14 (accessed: 27/1/2012).

[39] One example is the currently funded GAP2 project "Bridging the gap between science, stakeholders and policy-makers". cordis.europa.eu/fetch?CALLER=FP7_PROJ_EN&ACTION=D&DOC=51&CAT=PROJ&QUERY=012cee69e58c:4c12:3b6f8b90&RCN=99712 (accessed: 27/1/2012).

and people tearing up fields and so forth" (ibid. 76-77). Early engagement with the public, as a strategy intended to resolve such conflicts, would require seeing "what the issues are as soon as possible" (ibid. 57). As the interviewee clarified, "the rationale is try to involve stakeholders and interested parties at the time research agendas are drawn up, so that's instead of doing the research, develop the technology and then rolling it out and then finding out that you have got hostility from stakeholder-groups" (ibid. 81-84). Early engagement should "create a win-win-situation by involving all parties from the outset" (ibid. 85). This approach may lead to different technological solutions: "It may well be that the original research based agenda might not be the same that is adopted after this process, it may be modified, but if you modify (…), what was originally thought to be a good idea, you avoid impasses or total hostility and that's pretty in (…) everyone's interest" (ibid. 86-89). Early engagement is considered, as described by another interviewee, as a means of avoiding a blockage: "if things are developing without contact between these various factors you end up in a situation where there is a point of no return. You know because you have invested a lot in one direction you know just to drop it or to go back, so it's a bit guerre de tranchées, nobody can progress when it is like that, very early if you succeed to have time of co-construction of research agenda and co-construction of a common vision for common future then it becomes more easy, it is much easier to develop things without too much misunderstanding" (i: 69.75). Nanotechnology, stem cell technology, nanoparticles in consumer products, and synthetic biology would all be examples for technological areas "where there may be very good grounds for canvassing public opinion and understand what's involved" (h: 60-61). However, involving the public would not be about getting it "to blindly accept new technological developments but it was to find ways of creating a channel through which the public could start to express its opinion, positive or negative, on the development of emerging technologies" (ibid. 48-50).[40]

In contrast to the so called deficit model, the idea of early engagement is based on a concept of public, in which, as an interviewee made clear, laypeople are not to be converted or educated but listened to: "the public isn't just an empty vessel waiting to be filled with scientific information and they would passively accept it. (…) It was realized that scientists need, or needed and still need, to be much more aware of how the public thinks, because the public is not trained to think in a scientific way. Nonetheless, that does not mean that their way (of) thinking is in any way inferior and sometimes scientists forget that. What might be an interesting scientific solution to a problem might be totally morally and ethically unacceptable, and therefore it is advantageous for scientists to know about these issues, and before they try to seek public money to fund, or any money to fund projects and then identify that (…) the work that they have done (…) attracts hostility. And therefore the objective of that call (in which the project XENO got funded, EG) is to try to bring the scientist and the public together in a two-way communication-process" (ibid. 178-189).

[40] For the different approaches of citizen involvement as public relation or actual participation see also the OECD case study.

Table 2: FP4 1994 – 1998

Project	Duration	EC Contribution in Euro	Lead Country	Program	Contract Type	Number	Link
Installation of a European Centralized Facility for Preclinical Evaluation of Immunotherapy in Nonhuman Primates	1996-1998	n.a.	Netherlands	BIOMED2	Coordination of research actions	BMH4960127	http://cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_LANG=EN&PJ_RCN=2683329&pid=0&q=62447073E8D4A383BA85C17696FB2F7D&type=sim
Xenotransplantation – strategies for the prevention of carbohydrate related (hyperacute) rejection	1997-2000	1.500.000	Sweden	BIOTECH2	n.a.	BIO4972242	http://ec.europa.eu/research/biotech/biotech2-vol3/5-1-05-sub_en.html
Characterization of porcine complement regulatory molecules; application to xeno	1998-2000	n.a.	UK	Training and Mobility of Researchers	post-doctoral research training grants	FMBI972590	http://cordis.europa.eu/tmr/src/grants/fmbi/972590.htm
Xenotransplantation: ethical, social, economic and legal aspects	1998-2000	n.a.	Germany	BIOTECH2	ELSA	BIO4-CT98-0512	http://ec.europa.eu/research/biosociety/research_projects/xenotransplantation_en.htm
Glycoimmunology: synthesis and biological activity of immunoreactive glycocojugates	1996-1998	n.a.	Netherlands	BIOTECH2	Coordination of research actions	BIO4950004	http://cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_LANG=EN&PJ_RCN=2901296&pid=0&q=B284DAAAEE416F50BA7A89DABA169838&type=sim

Table 3: FP5 1998 - 2002

Projects	Duration	EC Contribution in Euro	Lead Country	Program	Contract Type	Number	Link
Establishment of novel targets for risk assessment and monitoring of xenogeneic infections in the course of animal to human transplantation (XENODIAGNOSTICS)	1999-2000	25,000	Germany	LIFE QUALITY	Exploratory awards	QLK2-CT-1999-40210	http://cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_RCN=4673365&CFID=8981167&CFTOKEN=51089429
Pathogenesis, epidemiology, immunopathology, and diagnosis of post-weaning multisystemic wasting syndrome (PWMS): an emerging disease of swine due to new porcine circovirus (PCV2). Development of recombinant vaccines	2000-2003	1,199,467	Spain	LIFE QUALITY	RS	QLK2-CT-1999-00307	http://cordis.europa.eu/life/src/control/qlk2-ct-1999-00307.htm
Study of the adhesive interaction between human and pig cells via daf/cd97; significance in xenotransplantation	2000-2001	54,504	Spain	LIFE QUALITY	Research grants (individual fellowships)	QLK3-CT-1999-51523	http://cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_RCN=5098258
Increasing public involvement in debates on ethical questions of xenotransplantation (XENO)	2002-2004	245,500	Austria	HUMAN POTENTIAL	Preparatory, accompanying and support measures	HPRP-CT-2001-00013	http://cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_RCN=5317361
Establishment of novel targets for risk assessment and monitoring of xenogeneic infections in the course of animal to human transplantation (XENODIAGNOSTICS)	2002-2004	262,000	Germany	LIFE QUALITY	Cooperative research contracts	QLK2-CT-2002-70785	http://cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_RCN=5699418

Table 4: FP6 2002 - 2006

Projects	Duration	EC contribution in Euro	Lead Country	Program	Contract Type	Number	Link
Engineering of the porcine genome for xeno studies in primates: a step towards clinical application (XENOME)	2006-2011	9,880,000	Italy	LIFESCIHEALTH	Integrated Project	37377	http://cordis.europa.eu/fetch?CALLER=FP6_PROJ&ACTION=D&DOC=1&CAT=PROJ&QUERY=012641d6a67c:7c77:3d09bbdc&RCN=84970
Study of the CD200/CD200R pathway in the pig-to-human setting to elucidate the molecular bases of xenograft rejection and develop approaches that promote xenograft survival (PORCINE CD200)	2006-2008	80,000	Spain	Marie Curie actions	Human Resources And Mobility	21293	http://cordis.europa.eu/fetch?CALLER=FP6_PROJ&ACTION=D&DOC=1&CAT=PROJ&QUERY=012c310fb8d5:e152:7da5f1e0&RCN=79038

Table 5: FP7 2007 - 2013

Projects	Duration	EC Contribution in Euro	Lead Country	Program	Contract Type	Number	Link
Impact of citizen participation on decision-making in a knowledge intensive policy field (CIT PART)	2009-2012	1,000,000	Austria	SSH	Small or medium-scale focused research project	225327	http://cordis.europa.eu/fetch?CALLER=FP7_PROJ_EN&QZ_WEBSRCH=SSH&QM_EP_PGA_A=FP7-SSH&QM_EP_SPA_A=SSH-2007-5.1-01&QM_EN_OC_A=&USR_SORT=EN_QVD+CHAR+DESC

7 Conclusions

This case study covers EU xenotransplantation policy from 1997 until 2009. In this period xenotransplantation was not subject to as fierce of a public dispute and scrutiny at the European level as other areas of biotechnology and biomedicine such as, e.g., GMO, BSE or human embryonic stem cells. On the contrary, the few accessible documents tell no story of controversy. The European Parliament did not debate the issue at any length. Only a handful of Members of Parliament addressed the subject in a few parliamentary questions.[1] The European Council briefly discussed xenotransplantation in the context of the clinical trials Directive.[2] Two scientific committees of the Commission, the SCMPMD and the SCHER dealt with the issue in their opinions. In addition, the Commission funded xenotransplantation research and ELSA projects in its successive Framework Programmes. The EMEA/EMA issued guidelines for xenogeneic cell based products in the 2000s.

In general, EU xenotransplantation policies can be characterized as enabling. The SCMPMD opinion was cautious but overall positive and framed xenotransplantation as one possible solution to organ shortage, mainly in cellular xenotransplantation. The clinical trial Directive established a compromise, which did not block clinical research altogether and left it to Member States to choose their own policies, thereby, in principle, allowing them to postpone decisions on clinical trials indefinitely. The European Council as well as the European Parliament and several of its Committees were involved in the codecision process, which led to this Directive. After this decision, EU policies became increasingly downstream and application oriented as well as technical. As Tallacchini observed, “the EU seem to be moving far from their former, more precautionary, position on (xenotransplantation), and to be adopting a more open view on the topic” (2002: 372). Rather than discussing “a moratorium on all clinical experimentation”, the focus moved towards “careful transnational monitoring, surveillance, and harmonization of standards” (ibid.). Consequently the EMEA/EMA established two documents, which defined standards providing guidance for potential applicants of market authorization; these reached throughout the entire xenotransplantation process, from animal rearing and husbandry to surveillance of human recipients, their close relatives and medical staff. The SCHER also contributed to the realization of xenotransplantation research by recognizing it as an area in which the use of NHP was deemed necessary. In addition, the European Commission actively supported xenotransplantation by funding it under the heading of “new therapies”. However, it also funded research in ELSA and participatory experiments therein. The public, however, was

[1] On 16 July 1997 Commissioner Cresson responded, for example, to a written Parliamentary question posed by Hiltrud Breyer whether the Commission would fund xenotransplantation research (E-1467/96) that no research was currently being carried out. The short response continues, however, that this does not “rule out such research in the future, as heterotransplantation is part of the work programme of research into medical bioethics”.

[2] The Swedish Presidency organized on 11 - 12 June 2001 together with the European Commission a conference on „Ethics and biomedical research – the process of balancing benefits and risks“ in Umea, Sweden. One of the three examples discussed at the conference was xenotransplantation. Xenotransplantation researchers as well bioethicists and a representative of a animal welfare organization gave presentations.

almost entirely absent in advisory and decision making processes leading to these policies, except for the SCHER's public consultation and hearing on the use of NHP in research in 2008.

Xenotransplantation was mostly put on the political agenda by scientific experts. The SCMPMD brought the topic to the Commission's attention as a future issue worthy of analysis. The EMEA/EMA dealt with xenotransplantation because it perceived regulatory gaps and recognized that firms were already developing products including xenogeneic cells. In contrast, the revision of a Directive on the use of NHP was put on the Commission's agenda by citizen's petitions and a European Parliament declaration. The topic of xenotransplantation was raised in this context by an external member of SCHER, but was only considered as a subordinated boundary area.

The limited xenotransplantation discussion at the EU level was mainly framed by organ shortage, the potentially associated risk of cross-species infection and how to contain it. Animal welfare was mainly discussed in the context of the use of NHP in research and proper breeding and husbandry.

The focus of discussion was strictly limited by the notion of sound science. In other words, though the available documents regularly acknowledge the validity of ethical issues, they exclude them with the very same regularity from the scope of their analysis and pass them on to other bodies, which are never clearly identified. The documents do not discuss the ethical acceptability of xenotransplantation in principle and hardly address the issue of public participation. Instead they take for granted that xenotransplantation is in principle ethically acceptable. As a consequence ethical, legal and social aspects were never comprehensively addressed by an advisory body of the Commission. However, they were addressed in several Commission funded research projects and participatory experiments. Yet, it seems that these were insufficiently linked to the Commission's advisory system and to decision making in the European Institutions.

The main everyday routines of policy making identified were procedures within the codecision process between the European Institutions and the European Commission's organized scientific advisory system. This process mainly becomes visible in official documents available at PreLex.

The European Commission exclusively used expert TA to get information and advice for its xenotransplantation policies. The impact of TA differed according to scientific body. The SCMPMD raised xenotransplantation on its own initiative without connection to a legislative activity; consequently it only had limited impact on policy making. In contrast, Borrás et al. consider the impact of the EMEA/EMA decisions as substantial overall (2007). The Commission's decision on the use of NHP in research was made before the final opinion

was adopted by the SCHER. However, the Opinion was in line with the Commission's general policy.

Although the European Union called for increasing citizen participation (Commission of the European Communities 2001, Abels 2002, Griessler 2011), the whole observable regulation process was, as has already been said, distinctly expert oriented. The working procedures of scientific bodies left little room for citizen participation. Citizen involvement was limited to the provision of well-measured information and a very strictly regulated and framed public consultation and hearing, which did not provide opportunities to raise questions on the ELSA of xenotransplantation.

The EU did not apply the tools of public consultation and citizen involvement in xenotransplantation policy making. As Tallacchini observed, the rhetoric of citizen participation remained "more (…) an intellectual exercise" (Tallacchini 2008:162). Citizens were defined as a lay public, stakeholders, patients and consumers and mostly excluded as active actors in policy making. Furthermore, citizens were allowed to retrieve provided information from the Internet and only admitted to public consultations and hearings if they accepted to ask purely scientific questions. Yet an animal welfare organization contested this narrow definition. The European Coalition to End Animal Experiments participated in SCHER's public consultation and hearing, challenged SCHER's expertise on animal welfare issues in regards to the research on NHP and entered a formal complaint to the European Ombudsman.

Participatory experiments, as already mentioned, were limited to research projects funded by the European Commission. During the last decade, PTA became a well-established method within the "Science in Society" program, which developed from methodological experiments into integrated projects, which emphasize mobilization and mutual learning of stakeholders in research and innovation. However, in the case of xenotransplantation there was no connection between these participatory experiments and actual advice and policy making in scientific committees and political bodies.

In recent years, the European Commission took several important measures to strengthen public trust in its regulation by emphasizing and increasing the independence, excellence and transparency of its scientific advisory committees. As a consequence the SCMPMD, EMA/EMEA and SCHER provided well-measured public involvement by allowing limited access to information, public consultations and hearings. Although the opening of scientific committees was a positive and significant step towards transparency and citizen participation, several important restrictions to citizen involvement in scientific committees exist and the power asymmetry between experts and laypeople is still enormously strong in favor of the former. Several factors are important in this context:

Xenotransplantation is a complex, transdisciplinary problem with repercussions, as has been shown, in many policy fields. The handling of such problems requires adequate complexity within an organization and therefore involves many internal and external actors. This turns citizen participation into a difficult problem and a substantial challenge for national governments. However, the task becomes even more difficult in the EU context with its multi-level system of governance and the different roles of the European Institutions therein. This not only poses an enormous challenge for European Institutions but also for European citizens. The number and complexity of EU Institutions, agencies and advisory bodies involved in xenotransplantation policies and their relation to one another appears to outsiders as an impenetrable labyrinth. Interested citizens would have to find out, e.g.: Who is competent for what in which area? When, where and how do important negotiations and decisions take place? Therefore it is very difficult for outsiders to keep track of, where and when, what consultations are carried out. This opaqueness, due to sheer complexity, poses a serious impediment for citizen participation.

Another problem concerns transparency. Although a number of quite successful attempts were made to increase transparency (e.g., by providing minutes, reports, decisions, information about expert recruitment), the insulation of the European Commission and the limited information it provides to outsiders still pose restrictions to transparency and citizen participation because available documents from European Commission Service, The Parliament, The Council, and scientific committees such as e.g., minutes, are often brief and do not provide much information to outsiders. Mostly they only inform about results of negotiations, not about the different positions actors were taking and the policy making process itself. European Council documents to which the public has access, e.g., do not justify a policy and do not explain why Member States decide to vote in a particular way. The tendency for insulation was more pronounced within the European Commission than in several other bureaucracies investigated in the CIT-PART project. Some interview requests to Commission staff and Members of Parliament were either denied altogether or were partly of limited value because civil servants of the European Commission are bound by confidentiality. This obligation also applies to members of scientific committees. Though understandable in relation to patent interests, this obligation also impedes citizen involvement and poses a severe methodological hindrance on social science research.

Citizen participation is also difficult to achieve because routine practices of scientific committees mainly take into account scientific experts. Once selected as members of a scientific committee, scientific experts make most of the important decisions such as recruiting working groups in a self selecting process, putting topics on the agenda, framing questions, consulting with the public, as well as drawing conclusions thereof.

Expert members of scientific committees in general are also in an advantageous position in comparison to citizens and NGO representatives because their activity in scientific committees is often part of their normal professional activity and supported by their

employees. In contrast, stakeholder representatives and citizens often lack the necessary funding to regularly participate in consultations and hearings.

This is connected to another problem citizen participation is facing currently, that is the strict framing of what is considered a valid problem in public consultation and public hearing according to the criteria of sound science. The focus on downstream oriented and exclusion of ethical questions, limits the scope of questions that can be discussed. According to an interviewee, stakeholder involvement would be problematic because it would bring conflicts of opposing groups into scientific committees, which cannot be solved by scientific methods (b: 235-242). However, these are also the sorts of questions, which are of concern to citizens. In addition, strict administrative requirements for public consultations and hearings turn public participation into a rather exclusive activity. Gender related problems were also never addressed in the documents.

Another problem public participation was facing is a lack of transparency of how the input of public consultations and hearings was dealt with. Citizens are currently not informed about the impact of their contributions on an opinion.

However, the perspective on public involvement is nothing but uniform within the European Commission. On the contrary, a diversity of policies seems to coexist regarding the challenge of citizen participation in science and technology policy. Whereas the routine practices within scientific committees and the codecision process were only participatory to a very small degree, the „Science in Society" Program advocated early involvement and engagement with the public. The European Commission funded research, which experimented with participation in science and technology policy. These activities, however, appeared to be rather disconnected from the scientific advisory system and decision-making in xenotransplantation policies. In summary, European xenotransplantation policies were directed towards safe implementation of the technology, whereas ELSA of xenotransplantation were hardly addressed. Public participation in xenotransplantation policies was discussed and experimented with, however, never actually applied in policy making.

8 Appendix

8.1 Political System

Legislature and **Constitutional Division of Territorial Power**:

The political system of the European Union (EU) is exceedingly complex because it is a multilevel system featuring a number of institutional actors and procedural routines functioning at each of its several levels. In order to deal with the task of coordinating the different levels, the EU quickly developed the principle of subsidiarity, i.e. the level where a problem arises should ideally also be responsible for solving the problem.

At the lowest level of policy making, communes and regions are represented in the EU Committee of Regions. As with all other institutional features of the EU, this does not prevent the actors who are represented in a certain institution from being simultaneously engaged in other institutions. In the case of the communes and regions, actors also contact the Commission directly in earlier and Parliament and national governments in later stages of the policy process. To this end, many regions (e.g. all nine Austrian ones) have a permanent representation in Brussels.

At the national level, most institutions important in the member states also make an effort to have their interests represented at the EU level also. In contrast to the representation of EU policy making in the mass media, national governments often do not speak with one voice in Brussels. Nevertheless, the most important institution representing national interests at the EU level is the European Council.

The Council of the European Union (commonly known as the Council of Ministers) has executive and legislative functions and is the EU's primary decision-making body; it is empowered to make decisions on any topic. However, it cannot propose laws, as this is the Commission's task. It is an institution that both defends national interests and acts as a collective system of decision-making. Its members are usually ministers from the member states. The Council has nine different configurations; depending on what policy issue is discussed, different ministers attend the meetings. Permanent representatives prepare the meetings and much of the work within the Council is done by them: by COREPER (Comité des représentants permanents) and by approximately 250 working groups that assist COREPER. All in all, the Council involves a great number of national officials, who meet at the level of the ministers' council, COREPER and at working group level.

The EU political system features, besides the Council of the European Union, also a second chamber, the European Parliament, of which the Council is the more powerful one.

The European Parliament is the only directly elected EU institution. It has

- supervisory power: it can supervise the Commission (rights to question, comment on and debate on reports) and to a more limited extent the Council (through assent),
- legislative powers: most of the decision-making today follows the codecision-procedure,
- and budgetary powers.

All of these powers have increased with each treaty. Especially the treaty of Lisbon strengthened the Parliament's role as the codecision procedure has since been extended to almost all policy areas. As in the US, detailed work is carried out by standing committees (Bomberg/Stubb 2008: 59) of which there are currently 20.[3] These are set up to prepare work for plenary sittings that are organized by policy area. The committees undertake (1) legislative work by analyzing draft legislations and writing amendments and (2) oversight activities. Each committee has a chairman, three vice chairmen and a Rapporteur, who is responsible for drafting the committee's Opinion or report. Committees provide the opportunity for individual members to have an impact on policies (Scully 2007:182).

The European Commission, the European Parliament and the Council of the European Union make the European Union's decisions. In principle, it is the Commission that proposes new laws but it is the Parliament and Council that adopt them. There are three forms of binding legislative acts the Union (Council alone or Council and Parliament in codecision-procedure) can pass: a regulation, which is a directly applicable law; a directive, which constitutes a framework of objectives which a national law must be based on to meet the stated aims; and a decision which applies only to a particular issue and is binding to whom it is addressed. Today, there are three procedures of decision-making within the European Union. The powers of institutions vary across them and they have changed with every treaty.

- Codecision: This is the procedure now used for most EU law-making. In the codecision procedure, Parliament does not merely give its opinion: it shares legislative power equally with the Council. If Council and Parliament cannot agree on a piece of proposed legislation, it is put before a conciliation committee, composed of equal numbers of Council and Parliament representatives.

[3] Foreign Affairs; Development; International Trade; Budgets; Budgetary Control; Economic and Monetary Affairs; Employment and Social Affairs; Environment, Public Health and Food Safety; Industry, Research and Energy; Internal Market and Consumer Protection; Transport and Tourism; Regional Development; Agriculture and Rural Development; Fisheries; Culture and Education; Legal Affairs; Civil Liberties, Justice and Home Affairs; Constitutional Affairs; Women's Rights and Gender Equality; Petitions; there are 2 special committees: Financial, Economic and Social Crisis; Policy Challenges.
2 Sub-Committees to the Committee on Foreign Affairs: Human Rights; Security and Defense;

- Consultation: The consultation procedure is used in areas such as agriculture, taxation and competition. Based on a proposal from the Commission, the Council consults Parliament, the European Economic and Social Committee and the Committee of the Regions. Parliament can approve the Commission proposal, reject it or ask for amendments. The Council examines the amended proposal and either adopts it or makes further amendments. In this procedure, as in all others, if the Council amends a Commission proposal it must do so unanimously.

- Assent: The assent procedure means that the Council has to obtain the European Parliament's assent before certain very important decisions are made. The procedure is the same as in the case of consultation, except that Parliament cannot amend a proposal. The assent procedure is mostly used for agreements with other countries, including agreements allowing new countries to join the EU.

Besides these three established procedures of policy making, several complementary (sometimes also alternative) forms of decision finding exist, some of them formal and some informal. On the informal side there is the increased cooperation between the European institutions, such as the “trilogues”, in which a few representatives of the Council, Parliament and Commission take part in order to resolve problems. Another example is the Open Method of Coordination, which was introduced in the early 2000s and in which the Member States can learn from each other and the tutelage of the Commission. In policy fields such as social policy and innovation policy a whole architecture of instruments has been developed in order to foster learning processes, e.g. workshops, conferences and meetings, trend charts comparing policies across countries and regions, exchanges of officials. At the formal end there are efforts to establish a Charter of Fundamental Rights in the Constitution, which has been ongoing for a long time but intensified in the 2000s.

The growing independence of the Parliament is not only based on the successive changes of the treaties and the concomitant expanding rights of the legislative body, but also on the expanding services of the Parliament. Besides the services provided by the institution itself (e.g. constitutional, legislative, scientific), each Member of Parliament has several personal aides, allowing for independent information gathering and subsequent maneuvering.

Cabinets and **Bureaucracy**:

The European Commission functions “somewhere between an executive and a bureaucracy” (Bomberg/Stubb 2008: 46). The Commission initiates policies, ensures the correct application of EU policies and manages European programs. It also manages and negotiates international trade and cooperation agreements (Egeberg 2007: 140f).

The Commission is divided into the College of Commissioners, which consists of 27 Commissioners who are responsible for one or more Directorate General and the

administrative Commission. The administrative Commission (bureaucracy) is made up of various directorate generals (DGs), each of which is headed by a director-general. These report directly to their relevant Commissioner[4]. Some DGs are further split into smaller units, dealing with specific topics. Task forces and interdepartmental working groups can also be created to allow for specialization. In practice it is difficult to draw a line between the College of Commissioners and the administrative Commission.

The Council proposes the Commissioners in cooperation with the president of the Commission, who is himself also proposed by the Council. Therefore, the College of Commissioners represents the composition of the member state governments regarding ideological orientation.

About 330 to 400 expert committees and about 150 standing advisory groups assist the Commission itself in its policy making processes. These committees complement the work done by the Commission's permanent staff.

The involvement of European-level interest groups is welcomed by the Commission to enhance legitimacy by discussing different interests on policy ideas. The Commission consults groups to draw on external resources for information and to learn about support or resistance to its proposals (Eising 2007: 208).

In the policy making process, the Commission has an initiative right and is then also responsible for the implementation of these policies.

- Right of initiative: The Commission is responsible for initiating and drafting policies. Other institutions may also initiate policies, but it is up to the Commission to draft a legislative proposal. Regarding matters of Common Foreign and Security Policy as well as Police and Judicial Cooperation, the right of initiating policies is not exclusive to the Commission; it therefore plays a lesser role in these areas. The Commission is involved in almost all stages of policy making, since it also plays the role of mediator between the Council and European Parliament. In practice, many initiatives coming from the Commission are responses to pressures from other sources. The Commission's 'own initiatives' thus account for only around 10-20 per cent of proposals (Bomberg/Stubb 2008:51).

- Implementation of policies: The Commission monitors the implementation of EU regulation in member states. EP/Council legislation often results in broad policy guidelines. It is the Commission's task to narrow these down by agreeing on more specific rules in the form of Commission directives and regulations, often called delegated legislation.

[4] There are 22 DGs that can be seen as equivalents of national ministries or government departments.

EU policies are administered by the Commission as well as by national and subnational authorities. Various agencies have been installed in recent years in order to cope with exceedingly demanding EU regulation. These agencies have different functions, responsibilities and structures (Dehousse 1997; Kreher 1997; Krapohl 2004; Gehring/Krapohl 2007; Christensen/Nielsen).

Executive-legislative Relationship:

The relationship between the EU institutions can be described as antagonistic. In as far as one wants to define Council and Parliament as legislative bodies and the Commission as an executive body, the relationship between executive and legislative has gone through changes throughout the history of the EU. In the 2000s the Commission, and to a smaller degree the Council, has increasingly come under pressure to open up its procedures so as to become more transparent, especially vis-a-vis the Parliament. Since the powers of the Parliament have grown even faster than those of the Commission, with each successive treaty revision, the Commission had to make concessions to the Parliament in the last years. An important right of Parliament is now that it may reject a new Commission, which has led to lengthy negotiations between the European institutions when the Barroso II Commission was installed in 2009. The Parliament is quite independent nowadays and it amends most laws that are presented to it by the Commission.

Party System:

The present parliament has 736 members from all 27 EU countries, which sit in political groups. The largest groups are comprised of identifiable political families such as the European People's Party (Christian Democrats) (EPP) and the Progressive Alliance of Socialists and Democrats in the European Parliament S&D. Other groups are more ad hoc and bring together loose coalition parties. The number of seats is currently distributed as follows:

- Group of the European People's Party (Christian Democrats) (EPP): 265
- Group of the Progressive Alliance of Socialists and Democrats in the European Parliament (S&D): 184
- Group of the Alliance of Liberals and Democrats for Europe (ALDE): 84
- Group of the Greens/European Free Alliance (Greens/EFA): 55
- European Conservatives and Reformists Group (ECR): 55
- Confederal Group of the European United Left - Nordic Green Left(GUE/ NGL): 35

- Europe of Freedom and Democracy Group (EFD): 32
- Non-attached (NA): 26

By and large the composition of the European Parliament reflects the swings of the elections to the national parliaments, which by itself is notable as it shows that the elections to the European Parliament are often more national than European in nature.

Interest Group System:

Originally the complex political system of the EU (respectively EEC, EC) included a number of characteristics known from corporatist systems, allowing, at least in theory, for a privileged access of employers' and employees' associations to the Commission. Especially the French socialist Jacques Delors, while he was head of the Commission, made an effort to strengthen the European Economic and Social Committee (EESC), which is an institution consisting of representatives of civil society (Wessels 2007, 669), but also the social partners themselves on the European level.

From the early years of the EEC onwards, the second important structural element of the political system of the EEC/EC/EU was the existence of a multitude of access points for external interests, allowing for a large and indeed increasing number of interest groups. Several thousand of these organisations have permanent offices in Brussels and try to influence policy making processes. Most interest groups are sponsored by industry and economic interests, especially firms, have a larger weight in Brussels than those of other parts of civil society.

Another type of interest representation has grown in importance since the 1980s, the regions. The Maastricht Treaty established the Committee of Regions, which since then has served as a forum of interest representation for their interests of communes and regions.

Judicial Review:

The European Court of Justice (ECJ) is the final arbiter in disputes among EU institutions and between EU institutions and member states. It pushed the integration process forward and, according to some scholars, its decisions contribute to the slow conversion of the Treaty of Rome into a constitution (Bomberg/Stubb 2008).

Some of the ECJ's decisions on trade have a great impact on the single market. Its rulings have also shaped national policies and have contributed to the claim that the Court has become a policy making body.

Direct Democracy:

Instruments of direct democracy have been discussed for several decades, as of now to no avail. In the discussions around the Charter of Fundamental Rights of the EU, the proposed (and failed) EU Constitution as well as the ensuing Treaty of Lisbon, instruments of direct democracy were discussed, with the proposals for referenda in particular becoming more concrete.

Political Culture:

For a number of years the missing demos has been decried by analysts of the EU as a key problem of the democratisation of the Europeanization process (Puntscher-Riekman 1998). This is the case not only because there are no Europe wide instruments of direct democracy or mass media, but, more importantly, that there is no European civil society. Most NGOs have their national powerbase and, at the most, a European head office in Brussels.

Since the 1990s the European institutions have been strengthening their efforts to open up policy making. The Council was relatively more unsuccessful in these efforts, as were the Parliament and the Commission. Especially the latter would be of importance for strengthening civil society because it is in the early phases of the policy making processes that are controlled by the Commission when access to policy making at the European level is relatively easier than in later phases. Yet, for several reasons, amongst them the missing resources of civil society at the European level and established political practices favouring industrial interests, participation at the European level has a tendency to strengthen the strong (economic interests) and dilute the weak (civil society interests). Especially smaller NGOs therefore still have a tendency to try to influence national governments in order to have an impact on European policy making via the national level.

Science-Society Relations:

EU public health governance is increasingly focusing on the management of risk because of new technological possibilities and some past failures in risk governance, e.g. BSE, GMOs. This has lead to public mistrust and the importance of expert and stakeholder consultation was recognized in order to legitimize the governance process.

From the late 1990s onwards, the EU aimed to strengthen the relationship between science and the public by supporting measures such as public consultation, public debates and public involvement in decisions about new technologies and innovation (e.g. Commission of the European Communities 2001). But the ways in which citizens and NGOs are involved remain underdeveloped (EC 2007b). Scientific expertise is very important.

Electoral System:

The electoral system of the EU, i.e. for the Parliament, is proportional (since the Maastricht Treaty). It is however complemented by a score of national rules, e.g. on minimal threshold levels (mostly 4 or 5%), minimal voting age (mostly 18 and 21), the allocation of seats (mostly after the d'Hondt system).

Over the course of its existence the European Parliament has tried to obtain the rights of a typical national parliament, including the ways of decision finding inside the institution. This led to a change from a strong personal mandate, in the sense of a high degree of independence of each Member of Parliament, to a strengthening of the European level parties, which was of key importance for making the institution's means of interest accommodation effective and a concomitant weakening of minority rights.

8.2 Policy Field

Cabinets: did they have a role in the policy field for the problems handled by e.g. the bureaucracy?

Though xenotransplantation policies did not involve many activities at the EU level, the Commission was involved in various ways, such as in the clinical trials Directive and the use of NHP in research.

Legislature: did it have a role (if yes, which chamber) in the policy field for the problems tackled by e.g. the bureaucracy?

The European Parliament was involved in the co-decision procedure of the clinical trials Directive (see 4.1) as well as Directive 2001/83/EC (see 4.2.1) and Regulation (EC) No 1394/2007 (see 4.2.2).

Executive-Legislative Relationship: is there a history of adversarial relations between executive and legislative in the policy field (e.g. over leadership on issues, media attention)?

There are few indications of a controversy between The European Parliament, the European Commission and the European Council in the matter of xenotransplantation (see party system).

Bureaucracy: are there specific units, which have dealt with the policy problem at hand; is there any cooperation with other political actors?

Several units such as DG SANCO, DG ENV, DG03 as well as EMEA/EMA were concerned with the topic of xenotransplantation.

Judicial Review: what is the tradition of law (Common/Roman); are the courts important for the policy field?

There were no court decisions in the area of xenotransplantation policies.

Party System: were some parties represented in Parliament interested in the policy field (e.g. the Greens)?

Xenotransplantation was in general hardly discussed in the European Parliament. The Greens posed parliamentary questions to the European Commission indicating criticism (E-14746/96, E-4098/07). Also an S&D Member of Parliament posed a question in the context of using wild caught baboons (P-3227/98). In 2010, a member of the Group of the European People's Party asked the Commission about the progress of the XENOME project (E-9429/2010).

Interest Group System: were some interest groups involved in the policy field (e.g. pharmaceutical industry, Chamber of Commerce, professional associations)?

Scientific experts were involved in policy making by giving scientific advice. Information about influence of interest groups was not available.

Political Culture: has civil society been involved in the regulation of XTP or in similar problems; how open is decision-making in this policy field?

Decision making was rather closed in the area of xenotransplantation, as it was in the area of human embryonic stem cell research in the context of the Sixth Framework Programme (Griessler 2011).

Science-Society Relations: what is the role of scientific experts in this policy field?

see interest group system

Direct Democracy: were there attempts to use instruments of direct democracy in the policy field (e.g. petitions on GMO, BSE)?

Letters were sent to the Commission opposing the use of NHP in research.

Constitutional Division of Territorial Power: were some regions more active than others in the policy field (e.g. in the form of funding programmes, regulations)?

n/a

Demand for XTP: are there interest groups asking for XTP (scientists, pharmaceutical industry, patient organisations etc.)?

Scientists raised the topic as an important future issue; other scientists applied for research money within the Framework Programmes.

State-EU Policy Relationship: how do EU policies enter and affect the political system ("download of policies"); how do national policy initiatives enter and affect the EU ("upload of policies")?

The clinical trial Directive was translated into national law by Member States. The EMEA/EMA guidelines are referred to in Member States.

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8.4 List of Interviews

a. European Commission, 1.3.2011, Brussels

b. Researcher 10.3.2011, telephone interview

c. Scholar in Jurisprudence, 2.12.2010, telephone interview

d. Researcher, 18.11.2010, telephone interview

e. European Medicines Agency, 23.12.2010, Vienna

f. Researcher, 17.11.2010, telephone interview

g. European Commission, 2.3.2011, Brussels

h. European Commission, 1.3.2011, Brussels

i. European Commission, 15.4.2011, telephone interview

j. Written response, 19.04.2011

8.5 List of abbreviations

AIDS	Acquired Immune Deficiency Syndrome

ATMP	advanced therapy medicinal products
BSE	Bovine Spongiform Encephalopathy
CAT	Committee for Advanced Therapies
CDBI	Steering Committee on Bioethics
CDSP	Committee of Ministers, European Health Committee
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
CoE	Council of Europe
COREPER	Comité des représentants permanents
CPMP	Committee for Proprietary Medicinal Products
CVMP	Committee for Medicinal Products for Veterinary Use
DG	Directorate General
DG ENV	European Commission Environment Directorate General
DG SANCO	Directorate General for Health and Consumers
EC	European Commission
ECEAE	European Coalition on the End of Animal Experiments
ECJ	European Court of Justice
EMA	European Medicines Agency
EMEA	European Agency for the Evaluation of Medicinal Products
ELSA	Ethical, legal and social aspects
EP	European Parliament

EPP	European People's Party
EU	European Union
FP	Framework Programme
GMO	Genetically modified organism
HMPC	Committee on Herbal Medicinal Products
NGO	Non Governmental Organisation
NHP	Non Human Primates
OECD	Organisation for Economic Co-operation and Development
PDCO	Paediatric Committee
PERV	porcine endogenous retroviruses
PTA	Participatory Technology Assessment
S&D	Progressive Alliance of Socialists and Democrats in the European Parliament
SCCS	Scientific Committee on Consumer Safety
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHER	Scientific Committee on Health and Environmental Risks
SCMPMD	Scientific Committee on Medicinal Products and Medical Devices
TA	Technology Assessment
WHO	World Health Organization
w. d.	without date

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