In the Shadow of Doctor Moreau: A Contextual Reading of the Proposed Canadian Standard for Xenotransplantation

Melanie J. Mortensen*

PRESCIENT SELECTIONS FROM the century-old H.G. Wells novel *The Island of Dr. Moreau* provide rhetorical echoes for this critique of the *Proposed Canadian Standard for Xenotransplantation*. Xenotransplantation, which is animal-to-human cell, tissue, or organ transplantation, represents one facet of the new areas of development that fall under the general rubric of biotechnology. This developing area has been slowed by the risk posed by infections that may emerge and threaten public health if clinical trials of xenotransplantation proceed. Xenotransplantation also has the potential of great profitability for the biotechnology companies that offer the source animals, particularly if the science should prove successful. This paper first introduces the scientific elements of xenotransplantation. Then, it surveys policy developments in Canada with respect to xenotransplantation. Finally, it turns to the ethical dimension of xenotransplantation, concluding that the nature of the risks and the precautionary principle should necessitate that Canada call for a moratorium on xenotransplantation.

DES EXTRAITS PRESCIENTS DU ROMAN du siècle dernier de H.G. Wells, *The Island of Dr. Moreau*, servent de fondement rhétorique à la critique de la Proposition d'une Norme canadienne pour la xénotransplantation. La xénotransplantation, qui est la transplantation de cellules, de tissus et d'organes d'animaux chez des personnes, représente une des facettes de cette nouvelle science que l'on appelle généralement la biotechnologie. Le développement de cette science est ralenti par les risques d'infection qui peuvent survenir et menacer la santé publique si les essais cliniques de xénotransplantation se poursuivent. La xénotransplantation, par ailleurs, représente une avenue prometteuse de profits très alléchants pour les entreprises spécialisées en biotechnologie qui offrent les sources animales, en particulier si la science s'avère fructueuse. Cet article fait d'abord un survol des éléments scientifiques de la xénotransplantation, puis passe en revue les politiques canadiennes élaborées en matière de la xénotransplantation. Enfin, l'article analyse les éléments éthiques de la xénotransplantation, puis, étant donné la nature des risques, conclut en appliquant le principe de précaution que le Canada devrait réclamer un moratoire sur la xénotransplantation.

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"As it happens, we are biologists here. This is a biological station—of a sort."

–H.G. Wells, *The Island of Doctor Moreau* (1896)[1]

INTRODUCTION

What could it mean? A locked enclosure on a lonely island, a notorious vivisector, and these crippled and distorted men?[2]

MANY RECENT BIOTECHNOLOGICAL advancements relating to human disease and health have received a great deal of attention because of the potential cures they offer for modern disease, the profits that may be made by the biotechnology industry and the money that may be saved by the government in medical costs. Nevertheless, there is a shadow of critique that seeks to draw attention to ethical considerations of the technologies, but is often subsumed by the market forces and the advancement of science. Xenotransplantation, which involves the transplantation of animal cells, tissues and organs into humans, offers the poten-

1. H.G. Wells, *The Island of Doctor Moreau: A Critical Text of the 1896 London First Edition, with an Introduction and Appendices*, ed. by Leon Stover (Jefferson, NC: McFarland & Company, 1996) at 84. The literary intrusions that appear are meant to remind readers of the horror with which the process of raising genetically modified pigs for xenotransplantation purposes might have been regarded some time ago. This novel strikes at the heart of the personhood debate that is, for the most part, overlooked with respect to xenotransplantation, but which is perhaps best exemplified today by the public outcry against human cloning. These excerpts are not meant to denigrate the technology of xenotransplantation, but to symbolize the shadow of ethical critique that may be and, indeed, has been raised with respect to the blurring of the line (rightly or wrongly) between humans and animals. Indeed, this novel is less fantastic in its imaginings than it is representative of the science of its era since "[a] huge and confusing literature arose in the late 1800s when experiments with skin xenografts were followed by the use of fragments of spleen, pancreas, nerve, thyroid and ovary taken from animals. Respectable scientists made reports of successful organ xenografting" (David Hamilton, "Reaching for the Impossible: The Quest for Tissue Replacement" in Leo C. Ginns, A. Benedict Cosimi & Peter J. Morris, eds., *Transplantation* (Malden, MA: Blackwell Science, 1999) 1 at 5).

2. Wells, *supra* note 1 at 90.

tial to save many lives that might otherwise be sooner lost due to shortages of donated organs. Xenotransplantation also poses a significant health risk not only to the patient, but also to the human species at large, as there exists a risk of viral escape in the transgenic cross.

While there have been policy initiatives in Canada with respect to this technology, the question remains as to whether they are adequate in regulating the development of this potentially hazardous procedure. If the lack of transplantable organs is driving the development of xenotransplantation, then the Canadian government, its public-health officials and regulatory bodies should first explore and develop initiatives to improve organ-donor rates, procurement and effective use. The government has indicated its commitment to such action, yet seems to be persuaded that xenotransplantation is the most promising alternative.

In addition to the unforeseeable nature of the public-health risks, the potential marketability of the xeno-organs is problematic. Canadian officials should not be deterred from placing stringent bioethical standards and regulations on the research and development of xenotransplantation. Canada requires explicit, rational and effective public policies and regulations that place bioethical concerns at the forefront, specifically including caution and higher standards of safety for both research and development of xenotransplantation. Canada also needs realistic analysis of the informed consent required by eventual research and therapeutic recipients and effective policy initiatives that would explore alternatives to xenotransplantation and would increase organ donation without the risk of infecting the general public. Ultimately, the Canadian government should ensure that it adheres to the precautionary principle regarding its treatment of xenotransplantation in its *Proposed Canadian Standard for Xenotransplantation*.[3]

Biotechnological advances pose new problems for bioethics: while the fundamental principles of bioethics persist, such as questions regarding informed consent and other related issues, the interventions of biotechnology make new considerations relevant. In general, one may argue that the marketplace for biotechnology within the medical and pharmaceutical fields changes the conceptual nature of the patient and of disease.[4] With respect to xenotransplantation, for instance, the urgent calls for development of the science are arguably based on humanitarian grounds, since the development of xeno-organs could help make up for the shortage of organ donors. However, the potential market demand for such xeno-organ products, procedures and related pharmaceutical support clearly provides incentives for biotechnology companies to downplay concerns regarding the inherent or potential risks in such research and procedures.

The disease of the patient requires a commodity—the xeno-organ—in order to be healed. In addition to a possible alteration in the sense of personhood that may arise as a result of these, as yet hypothetical and at best experimental,

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3. Health Canada, *Proposed Canadian Standard for Xenotransplantation* (Draft #14) by Andre La Prairie (Ottawa: Therapeutic Products Programme, July 1999), <http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/bgtd/xeno_std_e.html> [*Proposed Canadian Standard*].

4. See generally Bryn Williams-Jones, "Concepts of Personhood and the Commodification of the Body" (1998–1999) 7 Health L. Rev. 11, <http://www.genethics.ca/personal/CommodificationHLR.pdf>.

procedures, there is also the potential alteration or reduction of notions of humanity as well as the commodification of body parts and of the patient's disease (since the initial brave and compliant patients will be extremely valuable to biotechnology companies once clinical trials begin). Furthermore, to simply balance the shortage of organs against the development of a potentially infectious product that would require the sacrifice of animals is to effectively reduce the debate to one that too often simply balances the "pig" against the "peril"—or to one that balances the ethics of using potentially genetically modified animals for their organs against the risk of infectious disease. Indeed, the principles of bioethics are required more fundamentally in the context of xenotransplantation, since the focus of more closely applied ethics may be too narrow to effectively treat the larger philosophical issues that are raised by such experimental practices.

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1. XENOTRANSPLANTATION: OVERVIEW

> *Each of these creatures, despite its human form, its rags of clothing and the rough humanity of its bodily form, had woven into it, into its movements, into the expression of its countenance, into its whole presence, some now irresistible suggestion of a hog, a swinish taint, the unmistakable mark of the beast.*[5]

WHEN ONE FIRST HEARS of xenotransplantation, it seems like a fantastic notion. Even the word sounds fictional. Xenotransplantation refers to the transplantation of cells, tissues or organs from animal donors into humans.[6] The research and development of xenotransplantation is frequently cited as crucial because if it is found to be effective and practicable it could help to make up for the shortage of human organs available for transplantation. Pigs are currently being targeted as donor animals because there are biological and ethical problems associated with using non-human primates, even though (and, paradoxically, because) they genetically resemble humans.[7] The research and development of xenotransplantation has proceeded with more debate recently as a result of concerns regarding its risk of transmitting animal diseases to humans as a result of such transplantation, which diseases are sometimes referred to as xenozoonoses: "the transfer of infections by transplantation of xenogeneic tissues or organs … potentially poses unique epidemiological hazards due to the efficiency of trans-

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5. Wells, *supra* note 1 at 99.

6. See generally Ian F.C. McKenzie *et al.*, "Xenotransplantation" in Ginns, Cosimi & Morris, *supra* note 1 at 827.

7. See *e.g.* Jonathan S. Allan, "Nonhuman Primates as Organ Donors?" (1999) 77 Bulletin of the World Health Organization 62, <http://whqlibdoc.who.int/bulletin/1999/Vol77-No1/bulletin_1999_77(1)_62-81.pdf>. See also Jeffrey L. Platt, "A Primer on Xenotransplantation" in Jeffrey L. Platt, ed., *Xenotransplantation* (Washington, DC: American Society for Microbiology Press, 2001) 3 at 6:

> One reason for abandoning the use of non-human primates as a source of xenotransplants is that the number of primates potentially available as a source of organs and tissues does not approach the enormous number needed. Another reason relates to the risk of transmitting zoonotic agents from the primate to the human. Nor is it presently possible (and some would add that it is not ethical) to introduce genetic material into the germ cells of primates.

8. Fritz H. Bach *et al.*, "Uncertainty in Xenotransplantation: Individual Benefit Versus Collective Risk" (1998) 4 Nature Medicine 141 at 142, <http://www.nature.com/nm/wilma/v4n2.html>. See also Robin A. Weiss, "Transgenic Pigs and Virus Adaptation" (1998) 391 Nature 327, <http://www.nature.com/cgi-taf/DynaPage.taf?file=/nature/journal/v391/n6665/full/391327a0_fs.html&content_filetype=PDF> and Robin A. Weiss, "Retroviruses and Xenotransplantation" in Platt, *supra* note 7 at 239.

mission of pathogens, particularly viruses, with viable, cellular grafts."[8] Some ethicists and scientists, most notably Fritz Bach, have called for a moratorium on xenotransplantation until its risks have been more effectively determined.[9] While some critique the moratorium when the risk has not yet been assessed as creating "a dangerous precedent" and instead recommend caution,[10] those who ask for a moratorium have clarified that "a thoughtful and appropriate deliberative process, demanding a high degree of public engagement, must precede the clinical trials that reveal the risk."[11]

1.1. Xenotransplantation: The Science

> *You begin to see that it is a possible thing to transplant tissue from one part of an animal to another, or from one animal to another, to alter its chemical reactions and methods of growth, to modify the articulations of its limbs, and indeed to change it in its most intimate structure?*[12]

For xenotransplantation to be possible, the human recipient must withstand the rejection of the xenotransplant.[13] Without intervention, a xenotransplant recipient will undergo hyperacute rejection as a result of the xenoreactive natural antibodies that all humans have, which react with endothelial cells that line the donor organ's blood vessels; the xenoreactive natural antibodies "fix the complement, and it is the combination of the [antibodies] plus the activated complement that leads to rejection within minutes or just 1 or 2 hours."[14] Nevertheless, even if this rejection is reduced by either the block of the complement or the action of the antibodies, rejection may still follow in the next few days as a result of delayed xenograft rejection.[15] It has been suggested that the rejection is a result of the activation of the endothelial cells of the xenotransplant.[16] Indeed, much research is currently exploring ways of blocking this hyperacute rejection.[17]

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9. See Fritz H. Bach & Harvey V. Fineberg, "Call for Moratorium on Xenotransplants" Correspondence, (1998) 391 Nature 326. See also Margaret A. Clark, "This Little Piggy Went to Market: The Xenotransplantation and Xenozoonose Debate" (1999) 27 J.L. Med. & Ethics 137 at 147.
10. David H. Sachs *et al.*, "Xenotransplantation: Caution, but no Moratorium," Letter to the Editor (1998) 4 Nature Medicine 372.
11. Fritz H. Bach *et al.,* (Reply to Sachs *et al., ibid.*) (1998) 4 Nature Medicine 372 at 373.
12. Wells, *supra* note 1 at 135.
13. For an accessible explanation of the procedure and problems, see Health Canada, *Revised Fact Sheet on Xenotransplantation*, <http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/xeno_fact_e.html> [*Fact Sheet*]. See also Industry Canada, *Xenotransplantation Overview* (Ottawa: Life Sciences Branch, October 2000]. For an excellent survey of the science, see generally Platt, *supra* note 7. See also Donald V. Cramer & Leonard Makowka, "The Use of Xenografts in Experimental Transplantation" in Donald V. Cramer, Luis G. Podesta & Leonard Makowka, eds., *Handbook of Animal Models in Transplantation Research* (Boca Raton, FL: CRC Press, 1994) at 299.
14. Fritz H. Bach *et al.,* "Barriers to Xenotransplantation" (1999) 31 Transplantation Proceedings 1819 at 1819.
15. *Ibid.*
16. *Ibid.*
17. See Weiss, "Transgenic Pigs," *supra* note 8 at 327. Such strategies include the following: (1) to circulate "human blood plasma over αGalimmunoadsorbent columns to remove anti-αGal antibodies"; (2) "to inhibit triggering of the complement components or with excess amounts of a soluble form of complement receptor"; (3) "to generate transgenic pigs that overexpresses a fucosyltranserase that competes with the substrate for αGal attachment so that a fucose group, representing a natural human blood-group antigen, is substituted for αGal"; (4) "to knock out the pig gene that encodes α1-3 galactosyltransferase"; and (5) "to generate transgenic pigs that express human complement-regulatory proteins … [that] inhibit downstream steps in the complement cascade so that cell lysis may be prevented."

1.2. Early Trials of Xenotransplantation

> *I say I became habituated to the Beast People, that a thousand things that had seemed unnatural and repulsive speedily became natural and ordinary to me. I suppose everything in existence takes its color from the average hue of our surroundings.*[18]

Certain xenotransplantation trials have taken place with respect to human subjects, but until the problems with rejection have been overcome, routine xenotransplantation will likely remain only a hypothetical possibility and a subject of research, or at best an innovative therapy, rather than a standard therapeutic practice. However, given the rapid improvements in organ transplants over the last 50 years and the pace of recent biotechnological and genetic research and development, it is possible that xenotransplantation could become a relatively common procedure and that xenotransplants could become a marketable product as soon as the technology is adequately developed since governments—in Canada and elsewhere—and industry are, in general, cautiously committed to the eventual development of the technology.[19] Successful limited trials of xenotransplantation are being closely monitored for signs of infection. Jeff Getty, for instance, received a bone-marrow reconstitution using baboon lymphocytes and infection has not yet been reported; he has since become a xenotransplant advocate.[20] It has been noted elsewhere, however, that "[t]he monkey bone marrow failed to grow but the patient derived some benefit from the conditioning regimen used in preparing him for the procedure."[21] In Sweden, clinical pilot trials of xenotransplantation with porcine pancreatic islets and with extracorporeal pig kidneys have taken place and are being carefully monitored for infection.[22]

Throughout the development of transplantation research during the twentieth century, animal subjects were often a part of the experimental progression.[23] The use of animal subjects rather than humans in early transplantation experiments may reflect a former reluctance to use human cadaveric organs or the unavailability of human subjects as compared to animal subjects; since this has now become acceptable, the use of animal organs may seem comparatively less of an ethical barrier to overcome.

Early clinical trials with xenotransplantation have also been marked by a lack of full and informed consent. Perhaps the most famous of these is "Baby Fae," a dying baby girl who received a baboon heart transplant in 1984, and lived for three more weeks. The quality of her parents' consent has been cri-

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18. Wells, *supra* note 1 at 153–154.
19. See the discussion regarding Canadian biotechnology below at Part 4.
20. See A.S. Daar, "Animal-to-Human Organ Transplants—A Solution or a New Problem?" (1999) 77 Bulletin of the World Health Organization 54 at 56, <http://www.who.int/docstore/bulletin/pdf/issue1/organ.pdf>.
21. Allan, *supra* note 7 at 62.
22. C.G. Groth & M.E. Breimer, "Xenotransplantation in Sweden" (1999) 77 Bulletin World of the Health Organization 75, <http://www.who.int/docstore/bulletin/pdf/issue1/rtdiscussion.pdf>.
23. See David K.C. Cooper & Robert P. Lanza, *Xeno: The Promise of Transplanting Animal Organs into Humans* (New York: Oxford University Press, 2000) for a thorough survey of early xenotransplantation experiments.

tiqued, as has the judgment of the physician, Leonard Bailey.[24] Baby Fae was a baby who was born into an impoverished family, and her disease was used as the "primary justification for the experiment."[25] Leonard Bailey had been inspired by James D. Hardy, who had performed the world's first allograft lung transplant in 1963 and the world's first heart transplant in 1964, using the heart of a chimpanzee. The chimpanzee heart recipient, Boyd Rush, was poor and dying and was deaf-mute; he never consented to the procedure as he was "brought to the hospital unconscious and never regained consciousness."[26] His stepsister signed a consent form for the heart transplant, but it did not mention that it would be a chimpanzee heart.[27] Boyd lived for two hours after the operation.[28] In 1963, Keith Reemstma performed a transplantation of chimpanzee kidneys. The recipient, Jefferson Davis, was a poor and dying African-American man who lived for two months after the operation. When told that the chances would be one in a thousand and that the kidneys would be those of an animal, he reportedly replied, "Well, I ain't had no choice."[29]

The recitation of these circumstances of the recipients demonstrates the unsatisfactory nature of the consent in past experimental clinical trials of xenotransplantation. Nevertheless, the particular situation of each of these patients, whether because of their age or health or exacerbated by their economic situation, would make them vulnerable to providing insufficient consent for any treatment that might alleviate their desperate medical conditions.

1.3. Xenotransplantation and the Context of Organ Transplantation

> *"But," said I, "I still do not understand. Where is your justification for inflicting all this pain? The only thing that could excuse vivisection to me would be some application…"*[30]

In light of the dearth of transplantable organs, xenotransplantation is generally thought to be a positive development and is cast in noble and idealistic terms. For instance, it has been stated that it is "widely regarded as the earliest foreseeable means of alleviating the dire shortage of transplantable organs from human donors."[31] Such statements tend to presuppose the merit and necessity

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24. See George J. Annas, *Judging Medicine* (Clifton, N.J.: Humana Press, 1988) at 384: "Was Baby Fae a brave medical pioneer whose parents chose the only possible way to save her life, or was she a pathetic sacrificial victim whose dying was exploited and prolonged on the altar of scientific progress?" See also *supra* note 20 at 55: "Questions were asked about the adequacy of the information given to the parents. The surgeons were faulted for not looking hard enough for a human heart to transplant, and for being too optimistic." See also André Menache, "Stop Now Before It's Too Late" (1999) 77 Bulletin World of the Health Organization 76 at 77, <http://www.who.int/docstore/bulletin/pdf/issue1/rtdiscussion.pdf>, where it is indicated that "a proven surgical repair technique could have been used instead of the high-risk baboon heart. In addition, a human heart was available at the time. Also, the majority of medical opinion at the time was against the idea of using a baboon heart at all."
25. Annas, *supra* note 24 at 385.
26. *Ibid.* at 384.
27. *Ibid.*
28. *Ibid.* at 385.
29. *Ibid.*
30. Wells, *supra* note 1 at 137.
31. Harold Y. Vanderpool, "Critical Ethical Issues in Clinical Trials with Xenotransplants" (1998) 351 Lancet 1347 at 1347. See also the study presented by Roger W. Evans, "Coming to Terms with Reality: Why Xenotransplantation Is a Necessity" in Platt, *supra* note 7 at 29.

of organ transplantation. There is a perception that organ transplantation is an everyday therapeutic event, while the demand for organs as yet largely outstrips the supply. Many people die while on the waiting list for donated organs.[32] The lack of transplantable organs is therefore often described with an understandable sense of pathos and urgency.

The tragedy of the lack of transplantable organs is indisputable. Nevertheless, my concern is that there is little critical appreciation of the underlying basis for the nature of the biotechnological development. The definition of and explanation for xenotransplantation is in virtually all cases accompanied by claims that this science is required to help make up for the shortfall of organ donations. Nevertheless, only in the past 25 years has solid-organ transplantation become a more common occurrence with a reasonable survival rate. As with xenotransplantation, solid-organ transplantation is subject to problems of rejection, but this situation was improved with the development of immunosuppressive drugs such as cyclosporine. The unique characteristics of organ donation are that the recipient must wait until a suitable donor dies, that the organs are transplantable, that it is that particular patient's "turn" and that the organ remain in optimal condition until the transplantation. Thus, in addition to the problem of rejection, there are various issues that relate to organ procurement, supply and storage that would undoubtedly be alleviated by the development of xenotransplantation.

It was only in the past 25 years that organ transplantation became more standard practice, mainly due to the introduction in 1979 of cyclosporine, which reduced rejection.[33] The ethical, cultural and economic issues that were then a backdrop for organ transplantation may be revisited if the focus of development were to shift to xenotransplantation.[34] The ethical and cultural issues relating to the development of heart transplantation are similar to the basis for ethical debate regarding xenotransplantation.[35] They represent the need for society to become accustomed to and accepting of a scientific practice before its members will commit to donating bodily fluids and parts, either before or after death. Certainly, rates of organ donation could improve with better organ-procurement initiatives. But what difference would it make? Even if the organs are trans-

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32. Health Canada, *Proposed Canadian Standard*, *supra* note 3 at 1. By 1995, 40,000 people were registered on organ transplant waiting lists in the US (*ibid.* at 5). In 2000 in Canada, 147 patients died on waiting lists when no organ became available, while there were 1,882 organ transplants that year, and 3,700 on waiting lists (Health Canada, *Organ and Tissue Information Site: Facts and FAQs* <http://www.hc-sc.gc.ca/english/organandtissue/facts_faqs/index.html#stat>. See also the figures appearing in Industry Canada, Life Sciences Branch: *Biotechnology: Ethics and the Industry* "Xenotransplantation Discussion Scenario" (published online 24 October 2000, copy on file with the author) ["Discussion Scenario"]. The comparatively small numbers in Canada as compared to the United States suggest that the impetus for development lies beyond prolonging Canadian lives, and is perhaps more driven by the possibility for international marketability of xenotransplantation organs.

33. See Hamilton, *supra* note 1 at 15.

34. For a more explicitly expressed viewpoint regarding organ transplantation, see Andrew Trew, "Regulating Life and Death: The Modification and Commodification of Nature" (1998) 29 U. Tol. L. Rev. 271 at 310-311:

> Perhaps society more readily accepts the idea of organ transplantation. The shock of people walking around with parts from other dead people inside them has been muted. Maybe it is like long-term exposure to violence that might inure us to the shock of the new. However, even if we have overcome the revulsion at the mutilation of corpses for the benefit of others, we do so because gifts of organs suggest a good. The donation of organs is often spoken of as "the gift of life" or "part of me will live on." This softens the abandonment of the traditional propriety accorded the dead, which accompanies rituals for burial or last rites in almost all societies.

35. See Hamilton, *supra* note 1 at 14–15.

planted successfully at first, the chronic rejection of transplanted organs is still high.[36] Indeed, if there is such limited long-term success with human-organ transplantation, then surely the optimism regarding xenotransplantation, which faces considerably more biological barriers and hurdles, should be examined.

1.4. Marketing Xenotransplantation

> Then I heard the key turn in the lock, and Montgomery's voice in expostulation.
> "Ruin the work of a lifetime!" I heard Moreau say.
> "He does not understand," said Montgomery, and other things that were inaudible.
> "I can't spare the time yet," said Moreau.[37]

With transplantable organs, there is both demand and scarcity. The optimism that surrounds the development of xenotransplantation should therefore be regarded with skepticism, since biotechnology companies seem better positioned to reap the rewards of moving forward notwithstanding the risks involved —more so than the potential xenotransplant recipients and the greater public that would face the risk of potential xenozoonotic infection. Indeed, the faster that the science develops, the more time that biotechnology companies gain to profit from their patented materials and inventions. While it is certainly true that, if successful, the development of xenotransplantation may benefit the eventual recipients, the present biological barriers with respect to hyperacute rejection, the likelihood of chronic rejection and the risks of infectious disease indicate that any urgency regarding the development of xenotransplantation should not emanate from the Canadian government and its national health organizations.

The rapid and even urgent development of xenotransplantation may be attributed instead to the drive to patent, market and profit from xenotransplantation-related products such as the transgenic animals that may be created, the xeno-organs and the required pharmaceuticals. The "hype" that is generated regarding the potential benefits of xenotransplantation serves to increase investment in the research and development of the biotechnology companies involved, even though the successful implementation of the technology may lie in the distant future. Xenotransplantation ought to remain a distant possibility until the risks are better appreciated and the technology is fully regulated on a truly international scale.

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36. See Nicholas L. Tilney, "Chronic Rejection" in Ginns, Cosimi & Morris, eds., *supra* note 1 at 43:
> Despite…early successes, it has become clear that clinical transplantation has not yet achieved its potential as a long-term or permanent treatment for a life-long disease. In many patients, it provides no more than a short-term amelioration of the existing condition.

37. Wells, *supra* note 1 at 107–108.

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2. CANADIAN LEGISLATION AND REGULATIONS GOVERNING XENOTRANSPLANTATION

> *A kind of rhythmic fervor fell on all of us; we gabbled and swayed faster and faster, repeating this amazing law…. We ran through a long list of prohibitions, and then the chant swung round to a new formula:*
> *"*His *is the House of Pain."*
> *"*His *is the Hand that makes."*
> *"*His *is the Hand that wounds."*
> *"*His *is the Hand that heals."*[38]

IN GENERAL, THE LEGISLATION that governs therapeutic products is applicable to xenotransplantation, as is also the *Tri-Council Policy Statement* regarding ethical conduct for research involving humans.[39] The government has also indicated that xenotransplantation development should adhere to the programs of the Canadian Council on Animal Care and the guidelines for exclusion from xenotransplantation based on the criteria of the World Health Organization (WHO).[40] There has been a *Notice of Intent* issued by the Therapeutic Products Programme of Health Canada to the effect that a regulatory framework will be developed that will apply to xenotransplantation.[41] The Therapeutic Products Directorate "is responsible for the regulation of xenografts to ensure their safety, efficacy and quality before they are brought into use."[42] Researchers with Health Canada have indicated that "[g]iven that this is a new technology, specific guidelines are being drafted to ensure that appropriate safety standards and the necessary level of scrutiny are applied to any clinical trials."[43] These guidelines have since been drafted and their adequacy will be assessed below.

2.1. Xenotransplantation in Canada: Regulation and Policy

> *A series of propositions called the Law—I had already heard them recited—battled in their minds with this deep-seated, ever rebellious cravings of their animal nature. This Law they were ever repeating, I found, and—ever breaking.*[44]

Xenotransplantation is not prohibited in Canada. At present, the *Food and Drugs Act*[45] and related regulations would govern xenotransplantation, as

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38. Wells, *supra* note 1 at 118.
39. Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada & Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Ottawa: Public Works and Government Services Canada, 1998 with 2000 and 2002 updates), <http://www.ncehr-cnerh.org/english/code_2/> [*Tri-Council Policy Statement*].
40. *Proposed Canadian Standard*, *supra* note 3 at 13.
41. Health Canada, *Intent to Develop a Regulatory Framework for Xenografts* (Notice to Interested Parties) by Kim Hannah (Ottawa: Therapeutic Products Programme, February 1999), <http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/noi_e.html> [*Notice of Intent*].
42. Eileen S. Tackbarry & Peter R. Ganz, "Xenotransplantation: Assessing the Unknowns," Editorial, (1998) 159:1 Canadian Medical Association Journal 41 at 43, <http://www.cmaj.ca/cgi/reprint/159/1/41>.
43. *Ibid.*
44. Wells, *supra* note 1 at 150.
45. *Food and Drugs Act*, R.S.C. 1985, c. F-27.

xenografts would be considered to be therapeutic products and would meet the definition of a drug.[46] Xenografts and xenotransplantation may only proceed in authorized clinical trials, which would be governed by the *Food and Drug Regulations* section C.08.005,[47] and by the *Medical Devices Regulations* Part 3.[48] In a *Notice to Hospitals from the Therapeutic Products Programme*, Health Canada indicated that:

> [p]ursuant to these provisions, sponsors of clinical trials involving xenografts must send a submission to the [Therapeutic Products Programme, or TPP] of Health Canada for approval before a clinical trial may proceed. The TPP will require information regarding, among other things, the potential risks and benefits to the transplant recipient and also third parties, in making its assessment.[49]

Nevertheless, the TPP indicated that it was "not presently in a position to consider applications under the SAP [Special Access Program] for the use of xenografts, as it is not possible under SAP protocols to sufficiently evaluate evidence addressing the risks to third parties on an urgent basis."[50]

The clinical research involving xenotransplantation "should reference" the *Ethical Conduct for Research Involving Humans: Tri-Council Policy Statement*.[51] The *Proposed Canadian Standard* also suggests that, "[t]he use of animals for xenotransplantation should similarly reference the most current guidelines of the Canadian Council on Animal Care."[52] Nevertheless, the *Proposed Canadian Standard* indicates that "[i]n addition to the informed consent requirements of the Tri-Council policy, counseling, monitoring and informed consent requirements specific to xenotransplantation must be developed."[53] Furthermore, "[p]articipating centres and professionals should be cognizant of provincial and national legal requirements, and this Standard."[54] The binding nature of such standards and statements is a troubling issue.

Other legislation that is often not taken into consideration in discussions of xenotransplantation is the intellectual-property protection that would be

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46. *Supra* note 42 at 41.
47. *Food and Drug Regulations*, C.R.C., c. 870 (2001). <http://laws.justice.gc.ca/en/f-27/c.r.c.-c.870/125266.html>. Section C.08.005(1) provides the conditions required so that:

    > …a manufacturer of a new drug may sell it to a qualified investigator to be used solely for the purpose of clinical testing to obtain evidence with respect to the safety, dosage and effectiveness of that new drug...

    For the purposes of this paper, it is worth noting section C.08.005(3), which states that,

    > [t]he Minister may notify the manufacturer of a new drug that sales of that new drug to qualified investigators are prohibited if, in the opinion of the Minister, it is in the interest of public health to do so.

48. *Medical Devices Regulations*, S.O.R./98-282, s. 79, <http://laws.justice.gc.ca/en/f-27/sor-98-282/text.html>. This Part regulates medical devices for investigational testing involving human subjects. It applies to medical devices that are to be imported or sold for investigational testing involving human subjects.
49. Health Canada, *The Clinical Use of Viable Animal Cells, Tissues, or Organs to Treat Patients* by Dann Michos, (Ottawa: Therapeutic Products Programme), <http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/bgtd/noticetohospitals_e.html> [*Clinical Use*].
50. *Ibid.*
51. Health Canada, *Proposed Canadian Standard*, *supra* note 3 at 5.
52. *Ibid.* at 6.
53. *Ibid.*
54. *Ibid.*

afforded to the products of xenotransplantation. While patent-law considerations are for the most part outside the scope of this paper, it should nevertheless be noted that, even though such legislation does not govern the procedure or the clinical trials, there may be room to shape the best practices of xenotransplantation and its marketing. This might be achieved by controlling the patentability of the xenotransplantation-related products and by restricting the patentability and other intellectual-property protections afforded to those parties that comply with Canadian policy guidelines. Indeed, part of the problem with the lack of transparency of research and development of xenotransplantation arises from industry concerns about the protection of the intellectual property that is the basis for the products that they develop.

2.2. The Report of the Standing Committee on Health

> *Yet surely, and especially to another scientific man, there was nothing so horrible in vivisection as to account for this secrecy.*[55]

In April 1999, the Standing Committee on Health released *Organ and Tissue Donation and Transplantation: A Canadian Approach*, which recommended a public consultation on xenotransplantation.[56] Five months later, federal, provincial and territorial Ministers of Health agreed that they would create a National Coordinating Committee on Organ and Tissue Donation and Transplantation.[57] With respect to xenotransplantation, the only recommendations of the Report of the Standing Committee on Health were as follows:

> All research or other activities in the area of xenotransplantation must be open and transparent to the public. As well, the Medical Research Council, and any other federal granting body, must ensure that its researchers adhere to established standards.[58]

The government's response to this recommendation was:

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55. Wells, *supra* note 1 at 90.
56. Health Canada, *Fact Sheet*, *supra* note 13.
57. Health Canada, "Information: Government Response to the Report of the Standing Committee on Health, *Organ and Tissue Donation and Transplantation: A Canadian Approach*" at 2, <http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/bgtd/govresp_e.html> [*Government Response*]; Health Canada, *Transplantation: A Canadian Approach* (September 1999), <http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/bgtd/govresp_e.html> [*Transplantation*].
58. Health Canada, *Government Response*, *supra* note 57.

> In order to ensure openness and transparency, the names of the investigators, the titles of the research and the amounts awarded for research grants are available from the Medical Research Council (MRC). The MRC, along with the Natural Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC), published the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* in September 1998. It is the leading Canadian statement of policy in this area. The MRC and NSERC also founded the Canadian Council on Animal Care (CCAC) in 1968, and are its principal sources of funding. The CCAC sets the standards for all research involving animals. Funding from the MRC and the NSERC requires compliance with these policies. Health Canada is committed to continuing working in a transparent manner and will consult stakeholders and the Canadian public on this sensitive issue.[59]

This statement is interesting in that it demonstrates the limited nature of the information that is available to the Canadian public.

The general public may learn about the research, and Health Canada always invites public commentary on its publications with respect to xenotransplantation. However, there seems to be little room for entertaining the option of a moratorium on xenotransplantation. At best, there seems to be a willingness to adapt regulations according to the degree of public concern.[60] In other words, the public may be invited to comment, but such participation does not seem to affect policy when it does not accord with scientific progress or with industry and market prospects. In April 2000, Health Canada funded the Canadian Public Health Association, which formed a Public Advisory Group to conduct a public consultation on xenotransplantation.[61] The results of this report were later released, but these results do not appear on the Canadian government's information sheets about xenotransplantation. The number-one recommendation of the public consultation was: "That Canada not proceed with xenotransplantation involving humans at this time as there are critical issues that first need to be resolved."[62]

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59. *Ibid.*
60. See Health Canada, *Report from the Planning Workshop: Public Involvement on Xenotransplantation* (Ottawa: Therapeutic Products Programme, April 2000), <http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/bgtd/awsreport_e.pdf> [*Planning Workshop Report*]. This document reveals the lack of consensus and the difficulties even in determining the appropriate issues and manner of presenting information regarding xenotransplantation.
61. See Health Canada, *Fact Sheet*, *supra* note 13.
62. Canadian Public Health Association, *Animal-to-human Transplantation: Should Canada Proceed? A Public Consultation on Xenotransplantation* (Ottawa: Canadian Public Health Association, 2001) at Cover Letter to Minister, <http://www.xeno.cpha.ca/english/finalrep/reporte.pdf> [*Public Consultation Report*]. See Appendix 1 for the seven recommendations.

2.3. The National Forum on Xenotransplantation

> *"I see you look horrified, and yet I am telling you nothing new. It all lay in the surface of practical anatomy years ago, but nobody had the temerity to touch it. It's not simply the outward form of an animal I can change. The physiology, the chemical rhythm of the creature, may also be made to undergo an enduring modification, of which vaccination and other methods of inoculation with living or dead matter are examples that will, no doubt, be familiar to you."*[63]

Sponsored by the Therapeutic Products Programme of Health Canada and by the British biotechnology company Novartis, the National Forum on Xenotransplantation (the "Forum") assembled in November 1997 to explore the issues and to make policy recommendations with respect to xenotransplantation. The Forum included, as surveyed in the *Summary of Recommendations*, "doctors, ethicists, veterinarians, animal rights leaders, transplant recipients, public health officials, provincial representatives and federal regulatory authorities."[64] Indeed, the *Report of the National Forum on Xenotransplantation*[65] demonstrates the contributions of many of the significant figures in the field of xenotransplantation. The Forum included: plenary sessions that provided an overview of xenotransplantation; international perspectives; the scientific, medical and ethical issues; and clinical trials and surveillance issues. The Forum also included workshop reports. The findings from each of the workshop topics demonstrate the type of consensus and debate with regard to certain issues that arise in considering xenotransplantation and that are representative of much of the published work that deals with the technology.[66]

The Forum's workshop findings are significant because they consider the ethics involved in xenotransplantation in a more profound way than would a mere attempt to balance the shortage of organs against the development of a potentially infectious product that would require the harvesting of transgenic animal organs. Instead of treating xenotransplantation as an ultimately positive development with hurdles to overcome, the Forum entertains the possibility that a moratorium may be best if this is what the Canadian public would prefer. There is an appreciation of the various ethical problems associated with this technology, including the informed consent of the patients and the treatment of the animals. Furthermore, the Forum's recommendations with respect to policy, standards and regulations included the creation of regulatory bodies that would ensure that the ethics of xenotransplantation remain in focus.

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63. Wells, *supra* note 1 at 133–134.

64. Health Canada, *Viewpoint: A Summary of Recommendations from the National Forum on Xenotransplantation* (Ottawa: Therapeutic Products Programme, July 1999), <http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/forumsummary_e.html> [*Summary of Recommendations*].

65. National Forum on Xenotransplantation, *Report of the National Forum on Xenotransplantation: Clinical, Ethical and Regulatory Issues* (last modified: September 1998), <http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/bgtd/frmrptx_e.pdf> [*Forum Report*].

66. See Appendix 2 below. These recommendations provided therein mainly cite or are adapted from both the *Forum Report* and the *Summary of Recommendations* in order to provide a coherent, but brief, version of the recommendations for reference purposes.

2.4. The Proposed Canadian Standard for Xenotransplantation

> *"You see, I went on with this research just the way it led me. That is the only way I ever heard of research going. I asked a question, devised some method of getting an answer, and got—a fresh question. Was this possible, or that possible? You cannot imagine what this means to an investigator, what an intellectual passion grows upon him. You cannot imagine the strange colorless delights of these intellectual desires. The thing before you is no longer an animal, a fellow-creature, but a problem. Sympathetic pain—all I know of it I remember as a thing I used to suffer from years ago."*[67]

The *Proposed Canadian Standard* is meant to become the "criterion for clinical trials and regulation of xenotransplantation in Canada."[68] It contains the following sections: (a) a rationale for the consideration of xenotransplantation; (b) ethical principles; (c) an animal care and production program; (d) a procurement program; (e) a clinical xenotransplant program; and (f) adverse reactions/suspected infections. According to the "Preamble," the *Proposed Canadian Standard*:

> [a]ddresses the safety of viable animal organs and tissues for human transplantation purposes[;] … includes all aspects of care and humane treatment of the potential and actual animals, and the safety of recipients, personnel and others who may be exposed or affected by the transplant of animal tissue[;] … *defines the steps that must be followed in order to review xenotransplantation and determine if it can be performed ethically, successfully and safely in Canada* [;] … [and] *addresses the larger social, ethical and privacy issues of animal to human transplants on recipients and their families.* It is a dynamic Standard that will respond to current and future scientific knowledge and ethical principles in a timely fashion.[69]

While the *Proposed Canadian Standard* will become the criterion for clinical trials and for the regulation of xenotransplantation, it is still in draft format. Elsewhere, it has been noted that:

> The regulation of xenografts is closely related to the TPP's initiative for regulating human organs and tissues. Over the past several years, the TPP has worked with transplant programs, experts, and provincial and territorial ministries of health to develop strategies for improving the safety, availability and equitable distribution of organs and tissues for transplantation. A key component of the strategy is the Canadian General Standard on Safety of Organs and Tissues for Transplantation and a specific subset for xenotransplantation. These standards will eventually be recognized under the National Standards System of Canada and referenced in the appropriate Regulations…. Furthermore, the TPP is supporting the work of experts in the drafting of standards that will be used in the process to determine if clinical trials involving xenotransplantation can be performed safely in Canada.[70]

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67. Wells, *supra* note 1 at 141.
68. *Supra* note 3 at i.
69. *Ibid.* [emphasis added, original emphasis removed].
70. Health Canada, *Notice of Intent*, *supra* note 41.

At present, therefore, the standards-based approach is intended to be used to judge whether xenotransplantation clinical trials will be appropriate. However, it is not yet in place. Until then, xenotransplantation is governed by the *Food and Drugs Act* and *Regulations*, as well as by the *Medical Devices Regulations*. Sponsors must apply to the TPP for approval before a clinical trial with xenotransplantation may proceed, as discussed above with respect to governing Canadian law.[71]

The *Proposed Canadian Standard* implements some of the recommendations of the *Forum Report*. However, certain recommendations are not necessarily followed. For instance, the possibility of a moratorium, or of respecting the public's desire for the same, is overlooked. Instead, there is a list of conditions that would make the use of primates unethical—and only if it is judged unethical shall it be prohibited. Following a cursory mention of the ethical issues that arise in the use of pigs, there is the following rationalization:

> While the pig is an animal of sufficient intelligence and sociability to make welfare considerations paramount, there is no evidence that it shares capacities with human beings to the extent that primates do. As such, the adverse effects suffered by the pigs used to supply organs for xenotransplantation would not outweigh the potential benefits to human beings. *It is also difficult to see how, in a society in which the breeding of pigs for food and clothing is accepted, their use for life-saving medical procedures such as xenotransplantation could be unacceptable*.[72]

This passage exemplifies superficial compliance with the notion that ethics should guide the standards that are set for biotechnology research and development, but the *Proposed Canadian Standard* does not seem to demonstrate an objective treatment of the complex ethical ramifications of the research.

This lack of objectivity is problematic, especially given the claims regarding ethical principles that had been announced within the "Preamble." Indeed, there had been consensus from the Workshop on the Use and Care of Animals at the National Forum on Xenotransplantation that:

> [T]he use of animals is different, and not automatically justified because they are currently used for food, research, or other activities. Animals should be used only if other alternatives are not available. Alternatives include prevention of disease and maximizing the use of human organs. A review of the ethics of using animals for xenotransplantation needs to be discussed and wide public consultation is necessary. This needs to be done with appropriate education of the public to make an informed decision.[73]

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71. *Ibid*.

72. Health Canada, *Proposed Canadian Standard*, *supra* note 3 at 8 [emphasis added]. This sentiment is echoed elsewhere. See Arthur Caplan, "The Case for Using Pigs" (1999) 77 Bulletin of the World Health Organization 67 at 68, <http://whqlibdoc.who.int/bulletin/1999/Vol77-No1/bulletin_1999_77(1)_62-81.pdf>: "The fact that hundreds of millions of these animals are killed for food each year makes it difficult to muster moral outrage over their sacrifice to save lives."

73. *Supra* note 65 at 35.

At that time, the only signs of public consultation were the indications that "[a] public opinion survey was also conducted to help determine attitudes and knowledge of xenotransplantation."[74] However, the results of this survey do not appear to be available. The invitation to the general public to respond to the *Forum Report* or to the *Proposed Canadian Standard* seems to have been underplayed since the moratorium demanded by the *Public Consultation Report* is generally disregarded by the government in favour of the notion that the public be involved in the planning—rather than the obstruction—of the development of xenotransplantation. As such, this defies the *Summary of Recommendations* of the Forum, which recommended that "[i]t should be up to the Canadian public to decide whether animals ought to be used as sources of donor organs and tissues for humans."[75] The fundamental choice of whether xenotransplantation should precede at all in Canada seems to have been overlooked. The *Proposed Canadian Standard* instead ostensibly satisfies the Forum's recommendations by stating: first, that "none of these [alternative] approaches [such as improving health, improving the supply of human organs and tissues, and developing artificial replacements] could potentially relieve the worldwide shortage of organs;"[76] and, second, that

> … xenotransplantation presents issues of ethics which have not been agreed upon by public participation and consultation. It is therefore deemed essential that these [ethical] aspects be presented to the public for their input.[77]

If indeed the *Proposed Canadian Standard* "is intended to become the criterion for clinical trials and regulation of xenotransplantation in Canada"[78] and is already being established, there is little room for dissenting voices from the Canadian public to have any true influence.

Further problems with respect to the *Proposed Canadian Standard* arise from the mandatory nature of the criteria, the method by which the risk of infection is diminished and the lack of strict guidelines in relation to the non-compliance of researchers and industry. The *Proposed Canadian Standard* provides criteria for clinical trials and regulation, but the description of key requirements often seems to be discretionary instead of mandatory. For instance, while "the informed consent requirements of the Tri-Council policy, counselling [*sic*], monitoring and informed consent requirements … must be developed,"[79] patient consent "*should* always be sought and documented for xenotransplantation from a properly informed patient, and *should* include…" such information as the current status of xenotransplantation, potential risks, alternatives and information regarding the actual procedure.[80] Although the obligations of researchers to abide by these criteria may certainly be present—as informed-consent require-

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74. Health Canada, *Fact Sheet*, *supra* note 13.
75. Health Canada, *Summary of Recommendations*, *supra* note 64 at 4.
76. *Supra* note 3 at 2.
77. *Ibid.* at 4.
78. *Ibid.* at i.
79. *Ibid.* at 6 [emphasis added].
80. *Ibid.* at 7 [emphasis added].

ments are already provided by the *Tri-Council Policy Statement*—it nevertheless makes the standards seem more flexible than stringent.

The *Proposed Canadian Standard* provides that a xenotransplant registry should be initiated and supported that would "track patients and their contacts carefully for potential development of infections that present public health hazards…."[81] There is also a detailed protocol set forth to manage the reporting of adverse events, adverse reactions and suspected infections with respect to the organs or tissues. Furthermore, the conditions regarding informed consent recommend that the recipient's consent should include the "possibility of quarantine due to zoonoses."[82] However, many of the provisions relate only to the product, its eventual disposal and the reporting that is to be made regarding the adverse event. With respect to the recipients,

> Identified transmission of disease must be reported as described by provincial and federal health authorities. Notification of the source animal program, patient physician, physician declaring death (where appropriate) and to physicians involved in the transplantation of all the source animal organs/tissues must occur.[83]

Notification is mandatory in the event that there has been the potential transmission of disease, the appearance in a recipient of a reportable infection, the appearance in a recipient of a new cancer, a primary non-function of the transplanted xeno-organ and/or the death of the recipient.[84]

Thus, there appear to be strict notification requirements, but these criteria underline the lack of true control over, for instance, the number of human clinical trials that may proceed at any given time that might better manage the scope of any potential infection. This is only one example of a safety precaution that could have been inserted into the *Proposed Canadian Standard* and that would have reflected the risks involved in the procedure. The lack of greater controls that would limit the risk of infection may emanate from the fact that the Therapeutic Products Programme seems to find such a risk "remote."[85]

Furthermore, there is little consideration in the *Proposed Canadian Standard* for the consequences of non-compliance. The *Proposed Canadian Standard* indicates that a National Review Board of xenotransplantation should

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81. *Ibid.* at 31. For a practical discussion of the kinds of monitoring and study that would be required for the cautious progress toward xenotransplantation clinical trials, see Louisa E. Chapman, "Zoonosis as a Risk to the Xenograft Recipient and to Society: Theoretical Issues" in Platt, *supra* note 7 at 209:

> Life-long surveillance for clinical episodes compatible with xenogeneic infections is the major post-transplantation tool available to detect infections by agents that are not presently identifiable pre-transplant. The development of national or international registries would amplify the ability to recognize significant events by enabling epidemiologic surveillance of populations of xenograft recipients. Laboratory-based surveillance for endogenous retroviruses and other identifiable agents that cannot be removed from the xenograft can augment clinical surveillance. Laboratory-based studies of xenograft survivors will also increase our ability to quantify xenotransplant-associated risks and thereby expand our capacity to make science-based assessments of appropriate public policy.

82. *Ibid.* at 6.

83. *Ibid.* at 35.

84. *Ibid.* at 33.

85. *Ibid.* at 4: "[I]t is necessary to identify principles and procedures which can provide a basis for dealing with the *remote, and unquantifiable*, hazards that xenotransplantation could bring" [emphasis added].

be established and "should also advise on measures for monitoring of compliance to ethical commitments at the local level."[86] While Research Ethics Boards (REBs) have the authority to terminate research involving human subjects according to the *Tri-Council Policy Statement*,[87] compliance is of particular concern where the research that is conducted may not be transparent, or may be reviewed by ethics committees that may have conflicts of interest. In a controversial area like xenotransplantation it would seem difficult, if not impossible, for REBs to allow clinical trials to proceed ethically—particularly when it has been admitted that public consultation is required but has not been fully implemented or respected. Nevertheless, should xenotransplantation research or clinical trials proceed, there ought to be more stringent and explicit regulations with respect to non-compliance due to the ethical problems and infectious hazards that are involved.

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3. XENOTRANSPLANTATION AND ETHICS

> "But," said I, "the thing is an abomination—"
> "To this day I have never troubled about the ethics of the matter. The study of Nature makes a man at least as remorseless as Nature. I have gone on, not heeding anything but the question I was pursuing, and the material has … dripped into the huts yonder…."[88]

THE ETHICAL ISSUES THAT ARISE in the consideration and practice of xenotransplantation are often mentioned in passing, and may be summarized by subsection headings such as those that follow. Nevertheless, the ethical challenges posed by this technology are significant, and should be regarded as absolutely integral to any consideration of whether or how to proceed. The crude balancing of one interest against another is typical of many of the analyses of xenotransplantation. This is represented by, for instance, a simplification of the issues to merely an evaluation of whether the immediacy of the solution to the human-organ shortage should favour the interests of the pig more than the peril of infection.

Ethics should guide and infuse any development of the technology that takes place. Such ethical inquiries should therefore include both theoretical considerations and practical applications. Biotechnology is advancing more rapidly and is driven by profit motives in addition to medical demands. There is a great market demand for xeno-organs. The simplification of the ethical issues focuses the debate on the ethics of using animals and on the risk of infection, overshadowing the reason for the urgency, which may relate more to industry concerns than to health benefits.

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86. *Ibid.* at 9.
87. *Supra* note 39 at art. 1.2 at A.2.
88. Wells, *supra* note 1 at 141–142.

3.1. Xenotransplantation and Personhood

> *That these manlike creatures were in truth only bestial monsters, mere grotesque travesties of men, filled me with a vague uncertainty of their possibilities that was far worse than any definite fear.*[89]

When heart transplants were first introduced, there was a great deal of public apprehension.[90] They now seem to be socially and culturally acceptable. Much of the apprehension involved competing notions of what we considered it meant to be human. Similar concerns arise now with respect to the effect that xenotransplantation may have on notions of humanity and of human dignity.[91] While some suggest that religions may provide guidance, it has been noted that "modern interpretations of Judaism, Islam and other religions are not opposed to xenotransplants."[92] Even the *Proposed Canadian Standard* is cognizant of personhood concerns, and summarizes the basic issues as follows:

> Even if xenotransplantation were proven to be safe and effective, it challenges the basic integrity and intrinsic value of the human person and human species. Xenotransplantation may be viewed as further contributing to the "artificialization" of the human person and body. As xenotransplantation involves cells, tissues or organs from another species, it questions the very "nature" of what makes us human…. If seen as "unnatural," or against religious beliefs, recipients could be both personally stigmatized and socially ostracized from their families and communities…. Our homology, coevolution and interdependence with other species may be biologically evident but that does not necessarily make it ethically acceptable to foster the development of these techniques. This is especially so where the benefit is seen to be largely individual and the public risks high. Hence, the need for public consultation.[93]

The above passage is sensitive to the problems inherent in xenotransplantation. My concern is that scientific progress could entice the public to overlook these concerns, particularly when there are potentially "life-saving" techniques that may be developed. The public quickly seems to become habituated to scientific progress and to the presence of risk, as is evidenced by such examples as the initial quarantine of the astronauts after the lunar landings and

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89. *Ibid.* at 149.

90. Hamilton, *supra* note 1 at 14–15. See discussion above at text accompanying note 35.

91. The scope and length of this paper allows only a brief discussion of these issues of personhood, so the concerns will here only be introduced to provide context.

92. Vanderpool, *supra* note 31 at 1347. It should be noted that Vanderpool found that the preoccupation with such widely discussed issues overshadowed the critical and urgent issues related to the "ethical prerequisites to clinical trials with whole-organ and vasculated-tissue xenotransplants" (*ibid.*). This would therefore seem to be another example of the progress of science having suggested controls, but being superior to the concerns of the public, as the larger ethical concerns or potential philosophical objections become practically irrelevant.

93. *Supra* note 3 at 5.

the fears of infection with respect to the first uses of vaccines.[94] Nevertheless, there are some lines that the public seems reluctant to cross. It is for this reason that human cloning is considered unacceptable, and that many parties are concerned about the patentability of higher life forms, for instance.

Whether xenotransplantation crosses that line of public acceptance may depend upon its characterization by the media, by scientists and by governments. Not only does this technology contemplate transplanting animal cells, tissues and organs into humans, but it may also require genetically modifying animals with human genes. Such genetic modification thus blurs the distinction between humans and animals. Perhaps any discomfort regarding the creation of a type of modified humanized species of pig that would serve as a biological, medical product is meant to be alleviated by one's awareness that: first, the pig is clearly unlike the human; second, the pig would be serving to save lives; and, third, it serves as a source of food in certain cultures.[95] However, these considerations are not enough: "The broadest and deepest level at which we must consider the impact that xenotransplantation technology will have is on our societal-cultural paradigm—our shared story."[96]

3.2. Informed Consent

> *"And now," said he, standing up after a long gap of silence, during which we had each pursued our own thoughts; "what do you think? Are you in fear of me still?"*[97]

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94. See Jack M. Kress, "Xenotransplantation: Ethics and Economics" (1998) 53 Food & Drug L.J. 353 at 378:

    > Luddite fears of the future are natural, and by accounting for them properly, we declare that, while technological progress in medicine will clearly continue, but it will proceed cautiously. To ensure conformity with acceptable standards of risk-benefit analysis and overall safety, the following should occur: risk management systems should be developed and put in place to identify realistic concerns (both minor and catastrophic); ongoing projects should be closely and continuously monitored; and new evidence constantly should be digested, reassessed, reviewed, and accounted for to ensure that infectious agent detection, prevention, and management procedures remain appropriate for each specific xenotransplant application. It is not realistic to demand or expect a total absence of risk, but we can carefully balance the risks that do exist and weigh them prudently against the likely benefits to be achieved.

95. See *e.g.* Cooper & Lanza, *supra* note 23 at 194:

    > Our ethical qualms relating to the use of the pig as a donor animal are very much reduced in view of the fact that the pig is already purpose-bred as a source for food. Indeed, it has been suggested that the use of a pig as an organ donor—rather than a mere provider of meat—is a "nobler" use of the animal…. We would suggest that only the strictest vegetarians, who do not eat any form of animal tissue, do not wear leather shoes, and so on, can reasonably raise objections to the use of the pig in xenotransplantation.

96. Margaret A. Somerville, *The Ethical Canary: Science, Society and the Human Spirit* (Toronto: Viking, 2000) at 103. It is worth noting the rest of this passage in order to provide a sense of the spectrum of the ethical debate regarding personhood:

    > As was also true for human reproductive cloning, xenotransplantation raises issues related to our sense of identity. Does xenotransplantation take us yet one more step away from an integrated theory of personal identity and towards a modular theory of human identity—away from seeing ourselves as the unique, indivisible human being s that we are and towards seeing ourselves as simply a series of interchangeable parts? Or could the "miracle" that this technology makes possible deepen our awe and wonder about ourselves, our world, and life in general? In xenotransplantation, as is true of so many areas related to the new science, we need genuine, collective moral thinking and ethical exploration.

    See also Edmund L. Erde, "Paradigms and Personhood: A Deepening of the Dilemmas in Ethics and Medical Ethics" (1999) 20 Theoretical Medicine and Bioethics 141; see also *supra* note 4.

97. Wells, *supra* note 1 at 148.

Informed consent is required in order to perform any surgical medical intervention ethically. Therefore, with respect to xenotransplantation:

> [I]nformation about the nature of the proposed procedure and its attendant risks which a reasonable man in the patient's position would want to know, or which the doctor knows the particular patient would want to know, must be explained to the patient. In general the less necessary the procedure and the greater the risks, the more stringent is the content of the duty of disclosure. The doctor may reply [sic.] on the patient's consent as being valid if there is apparent, subjective understanding of this information by the patient.[98]

This is the "general rule." With respect to xenotransplantation, it would be satisfied with proper consent requirements as proposed by the *Proposed Canadian Standard* and by the requirements of the *Tri-Council Policy Statement.*[99] Another element of informed consent is that "the coercion naturally present in the doctor-patient relationship, and especially the doctor-dying-patient relationship, be recognized."[100] This would be particularly relevant in the case of organ xenotransplantation where the patient has no other option and where there are no human organs available. When treating prisoners, "a very high degree of care must be taken to counteract the coercive effects on consent, of the institutionalization and deprivation suffered by prisoners."[101] With respect to consent to xenotransplantation and child recipients, the principle should be respected that "except in extremely rare circumstances a parent may not consent to non-therapeutic, or more than minimal risk personally non-beneficial interventions on the child."[102] Innovative therapies may be ethically allowable for adequately informed patients when done for their personal benefit in "last-chance" interventions.[103] The fact that xenotransplantation may be used in trials under such circumstances and with patients who may be historically disadvantaged may, some argue, compromise the consent of the patient.[104]

What is unique about xenotransplantation are the special circumstances associated with this technology. Many of the concerns with respect to informed

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98. Margaret A. Somerville, *Consent to Medical Care*, Study Paper for the Law Reform Commission of Canada (Ottawa: Minister of Supply and Services Canada, 1979) at 112.

99. *Supra* note 39, arts. 2.1 to 2.8.

100. *Supra* note 98 at 113.

101. *Ibid.* at 114.

102. *Ibid.* at 113. See also D.W. Meyers, *The Human Body and the Law*, 2d ed. (Stanford: Stanford University Press, 1990) at 261:

> The parent or guardian has no legal or moral authority to authorize [non-therapeutic] treatment harmful to the child. One exception may be where the child is hopelessly and terminally ill. In such instances if the parent can authorize withholding life-sustaining treatment then certain non-therapeutic experimental treatment may be allowed, but only if it will *not* increase the pain or suffering of the child and it is fully consistent with his or her dignity as a person.

103. Bernard M. Dickens, "Legal and Regulatory Issues" (1999) 77 Bulletin World Health Organization 70, <http://www.who.int/docstore/bulletin/pdf/issue1/rtdiscussion.pdf>.

104. See *e.g.* Kress, *supra* note 94 at 372–374 and A.P.R. Aluwihare, "New Problems Beget New Solutions" (1999) 77 Bulletin World Health Organization 64 at 65, <http://whqlibdoc.who.int/bulletin/1999/Vol77-No1/bulletin_1999_77(1)_62-81.pdf>: "From historical precedent we can expect that terminally ill prisoners or poor people, who need transplantation but who have no hope of access to the best currently available, may be asked to be guinea pigs for xenotransplantation." See also *ibid.* at 72: "'[l]ast chance' interventions limited to treatment only of the most severe or hopeless cases, involving patients least likely to be helped, do not test a research intervention adequately."

consent to xenotransplantation relate to the risk of infectious disease and associated issues. The potential for an infectious virus to develop means that the xenotransplant recipient would need to be monitored for the rest of his or her life and would perhaps require quarantine; in addition, it has been advised that the patient consent to an autopsy.[105] Furthermore, the obligations to be monitored may infringe upon an individual's rights to privacy and mobility. Such issues have not yet been adequately resolved. Indeed, the nature of such obligations would surely take the patient beyond informed consent because it would be practically

> … impossible for patients to exercise their well-established legal right to withdraw consent for a health care procedure or participation in a medical experiment…. While it is probably legally inaccurate to view any informed consent mechanism as creating a binding contract, the required public health provisions will, on a practical level, have that effect.[106]

Further issues with respect to the nature of the informed consent of the patient include the contacts between, on the one hand, the patient and parties involved in the xenotransplantation surgery and treatment and, on the other hand, in the patient's daily life, since such close contacts (with sexual partners, for instance) would also require monitoring as a result of the risk that they might be infected through their interactions with the xenotransplant recipient.[107]

As discussed above, the risk of infection has been characterized as "remote, and unquantifiable" in the *Proposed Canadian Standard*.[108] This is an example of the risk of hazardous infection being dismissed or downplayed as being minimal; yet it has been noted that "it only takes one transmission from one baboon to a human to start an epidemic[;] [t]here's no way you can make it safe."[109] Greater knowledge of risk assessment has helped the US, for instance, to decide to allow further clinical trials, but "[i]n dealing with infectious risk, the

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105. See Patrick S. Florencio & Timothy Caulfield, "Xenotransplantation and Public Health: Identifying the Legal Issues" (1998) 90 Canadian Journal of Public Health 282 at 283, <http://www.xeno.cpha.ca/english/viewpnt/issues/legal/page1.htm>.

106. *Ibid.*

107. Margaret A. Somerville, "A Retrospective Overview of the Discussion of the Ethical Issues," (Closing Remarks in the Excerpts from the *Report of the National Forum on Xenotransplantation: Clinical, Ethical and Regulatory Issues*, 6–8 November 1997) 59, <http://www.hc-sc.gc.ca/hpb-dgps/ therapeut/zfiles/english/bgtd/frmrptx_e.html> at 61[*Retrospective Overview*].

108. *Supra* note 3 at 4.

109. See Menache, *supra* note 24 at 76-77, citing US veterinary virologist J.S. Allen's quote in a *Time* article (15 January 1996) at 40. See also Weiss, "Retroviruses," *supra* note 8 at 247:

> Overall, the factors concerning viral zoonosis in xenotransplantation are complex, and the risks are extremely difficult to quantify. The worst-case scenario would be a major new viral pandemic like HIV/AIDS. A more realistic scenario, to my view, is that, perhaps, 1 in 1,000 xenograft recipients may pick up a porcine retrovirus, and if detected, that infection should be treatable by anti-retroviral therapy.

reality is that our best efforts may decrease but will never eliminate risk."[110] Nevertheless, prior thinking about risk assessment in medical experimentation or in clinical trials with other technologies does not necessarily take into account the magnitude of risk that exists with regard to xenotransplantation. In other words, it may be true that a patient can consent to a certain degree of risk regarding his or her own body, but with xenotransplantation the difference is that "the risks not only are to the immediate subjects of the research, but also could be to the public at large."[111]

It has been argued by Fritz Bach, who has elsewhere called for a moratorium on xenotransplantation until the public has been consulted and has decided "whether it wishes to consent to clinical xenotransplantation at all,"[112] that:

> [t]he fact that the magnitude of the risk is not known does not justify proceeding in order to find out. The decision by the individual patient, and in the case of xenotransplantation by the public, must be made while realizing that the risk exists, even though we cannot quantify it.[113]

Bach's arguments point to the risk of infection that xenotransplantation might pose to third parties, which has led to suggestions that "community consent" or "societal consent" should be required.[114] This underlines the need to consult with Canadians before proceeding with xenotransplantation to any extent whatsoever.

3.3. Ethical Issues with Respect to Animals

> *Before they had been beasts, their instincts fitly adapted to their surroundings, and happy as living things may be. Now they stumbled in the shackles of humanity, lived in a fear that never died, fretted by a law they could not understand; their mock-human existence began in an agony, was one long internal struggle, one long dread of Moreau—and for what? It was the wantonness that disturbed me.*[115]

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110. F.A. Murphy, "The Public Health Risk of Animal Organ and Tissue Transplantation into Humans" *Science* 273:5276 (August 9, 1996) 746, <http://www.sciencemag.org/cgi/content/full/273/5276/746>. With respect to the danger of minimizing risk, Murphy states, "In evaluating the pathogenic potential of specific viruses, rather than whole categories … it will not be easy to determine which viruses represent a risk to the xenograft recipient alone, which represent a risk to society as a whole as a result of species jumping, and which may be dismissed as representing a minimal risk" (*ibid.*). Furthermore, other commentators note that there is a "logical inconsistency in the rules currently governing xenotransplantation"; see Fritz H. Bach, "Putting the Public at Risk" (1999) 77 Bulletin World Health Organization 65 at 66, <http://64.233.167.104/u/who?q=cache:zPotobUyRUwJ:www.who.int/bulletin/pdf/issue1/rtdiscussion.pdf+F.H.+Bach+1999&hl=en&ie=UTF-8>:

> The baboon as donor may well pose a higher infectious risk than the pig, but in fact we do not know the extent of the risk presented by either animal. Given this ignorance, is it not somewhat incongruous to conclude that the risk of using baboons is too great while the risk of using the pig is acceptable? From the ethical point of view, both pose a risk to society and it must be society that decides under which conditions it is willing to accept that risk.

111. *Supra* note 107 at 59.

112. Bach & Fineberg, *supra* note 9.

113. Bach, "Putting the Public at Risk," *supra* note 110 at 66.

114. See *e.g. ibid.* "[T]he tremendous potential risks associated with xenotransplantation arguably necessitate some form of 'societal consent' or a 'public mechanism for determining the acceptability of, and method of consent to, the risk.' " See also Daar, *supra* note 20 at 58: "Since the community is in a sense being put at risk, there is a real argument for considering some form of community consent as well…. [but] there is little experience in obtaining such community consent."

115. Wells, *supra* note 1 at 167–168.

Xenotransplantation clearly raises ethical issues with respect to the use of animals as the source for the xeno-organs. While the full treatment of this issue is outside the scope of this analysis of the *Proposed Canadian Standard* and has been ably and amply treated by philosophers and bioethicists alike, a brief overview of the concerns provides context for the argument at hand. The choice, breeding, care, treatment and disposal of the animals that would be used for xenotransplantation are important elements of the xenotransplantation discussion. This aspect of the debate is often balanced against the human interest. Thus, some point to the breeding of pigs for food as a justification for the seemingly morally superior potential that pigs may serve by saving the lives of humans.[116] However, this type of argument does not seem to consider the fact that these animals will have been genetically modified, and will most likely have been raised in unnatural, sterile conditions in order to be keep them pathogen-free.[117]

The ethics of using any animals whatsoever—pigs probably and primates possibly—for xenotransplantation must be more seriously considered in light of recent developments with respect to both animal-rights arguments and concerns regarding biodiversity. Furthermore, greater attention should be paid to the National Forum recommendation that animals should only be used as a last resort.[118] Since that is the case, it would seem logical that the Canadian government more actively pursue such alternatives as mechanical and artificial replacements in light of the precautionary principle in order to minimize the risks posed by xenotransplantation. The proposal of creating a new medical product such as xeno-organs requires much ethical debate.

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4. DOES THE CANADIAN GOVERNMENT GO FAR ENOUGH?

> *A horrible fancy came into my head that Moreau, after animalizing these men, had infected their dwarfed brains with a kind of deification of himself.*[119]

THE AMOUNT OF ATTENTION that the Canadian government has paid to xenotransplantation seems laudable. One hopes that this attention is indicative of public-health concerns, as well as of enthusiasm for the potential health benefits. However, biotechnology is an important industry for Canada; the rationale for proceeding quickly with any clinical trials should therefore be carefully examined. In order to provide a final assessment of the *Proposed Canadian Standard*, the initiatives of the Canadian government with respect to its policy formation on xenotransplantation should be set in a broader context beyond the common positions of the debate. While the duly elected Canadian government ostensibly responds to the concerns of the Canadian public and delegates certain responsibilities over decision-making with regard to the health and welfare of the public to trained and responsible administrators, scientists and ethicists, its agenda is not beyond

116. Health Canada, *Proposed Canadian Standard*, *supra* note 3 at 14. See also the discussion above, at text accompanying note 69.

117. Somerville, *Ethical Canary*, *supra* note 96 at 98.

118. *Supra* note 65 at 35.

119. Wells, *supra* note 1 at 119.

reproach or critique, nor should it be taken for granted that the Canadian government unquestionably acts in the best interests of the Canadian people.

The purpose of this article is not to criticize the Canadian government, nor to insist that the Canadian public should be regarded as the best arbiters of any "Canadian" position on xenotransplantation. Rather, it is to examine the *Proposed Canadian Standard* from a perspective distinct from the archetypal ethical arguments, to critique its leniency with respect to curtailing health risks and to present possible reasons as to why the Canadian government may create policy that is favorable to industry, yet appears less receptive to the input of the Canadian public and to valid concerns about public-health risks.

4.1. Alternatives to Xenotransplantation

> *Then we went into the laboratory and put an end to all we found living there.*[120]

It seems anomalous to provide the heading "alternatives" to xenotransplantation, since it would seem to imply that xenotransplantation is a foregone conclusion. Instead, I wish to emphasize the fact that human-organ transplantation is the accepted practice, whereas xenotransplantation is simply an alternative to this practice since the Canadian government has already committed to increasing the levels of organ donation.

The Ontario government recently proposed an initiative with regard to better procurement requests on the part of doctors when dealing with patients and the families of patients. These developments are encouraging. Nevertheless, it has been argued that human donors will never provide enough transplantable organs to meet the demand, even if procurement rates improve.[121] It is tragic that there is an organ shortage, but there must be better efforts concentrated on improving access to human organs because they are currently the more biologically sound choice. Indeed, as discussed above, even if organ-donation rates were to increase, there would still likely be problems with hyperacute and chronic rejection of the organ, as well as with the reoccurrence of the disease that caused the necessity for the organ transplant in the first place.[122] The Canadian government's initiatives toward reducing the need for organ transplants by focusing on the treatment of disease represent another positive step that could help to avoid the need for difficult biotechnology products such as xenotransplants. There should be more stringent controls on the development of xenotransplantation within Canada in light of the complications of this science and in light of the unpromising outcome for patients at present in comparison to the potential reduction of organ shortages that might follow the improvement in the procurement of organ donations, the reduction of both human-transplant rejection and the severity of diseases that give rise to organ failure, as well as the development of more effective artificial replacements.

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120. *Ibid.* at 178.
121. Health Canada, *Proposed Canadian Standard*, *supra* note 3 at 2 and 4.
122. See Tilney, *supra* note 36 at 43.

4.2. The Precautionary Principle

> *I am only beginning. These are trivial cases of alteration. Surgery can do better things than that. There is building up as well as breaking down and changing.*[123]

The Canadian government ought to apply the "precautionary principle" to the regulation of biotechnology. The precautionary principle refers to the "proposition of international environmental law which says that, in the face of uncertain risk and incomplete data, policy-makers should err on the side of restraint."[124] It is worth noting that the interpretation of the precautionary principle may also influence how it is applied in terms of policy. For instance, another commentator notes that the precautionary principle requires that,

> [W]hen faced with an unknowable and unquantifiable risk that cannot be ruled out, actions should be taken in advance to minimize that risk. Protocols for research and clinical trials, and certainly for regular practice, need to be carefully developed and applied so that all reasonable health and safety issues are fully taken into account.[125]

In the first analysis, a moratorium would seem to be appropriate; in the second, the *Proposed Canadian Standard* and related Canadian attention to concerns regarding xenotransplantation would seem to be satisfactory. These two options reflect the basic problem with respect to Canada's further action regarding xenotransplantation. Both a moratorium on xenotransplantation and the cautious development of clinical trials of xenotransplantation would seem to heed the precautionary principle.

Nevertheless, the precautionary principle not only applies to the action that should be taken in advance of the establishment of certainty with respect to risks, but also requires that the burden of proof "should lie with those developing the technology to demonstrate that it will not cause serious harm."[126] It has been noted elsewhere that the unknown risks of xenotransplantation require that the burden of proof be placed on

> …those who wish to undertake xenotransplantation…to show that this is both *reasonably safe and ethical*. This means that if there is equal doubt as to whether either of these requirements is fulfilled, xenotransplantation research on humans cannot proceed until this doubt has been resolved in favour of proceeding.[127]

At least such an approach could settle the debate as to how to proceed at the present time with respect to undertaking clinical trials in Canada. Since stakeholders like, for example, the biotechnology companies have such profits to gain from the rapid development of the technology, their interest in proceeding

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123. Wells, *supra* note 1 at 132.
124. Clark, *supra* note 9 at 147.
125. Kress, *supra* note 94 at 378.
126. J. Hughes, "Xenografting: Ethical Issues" (1998) 24 J. Med. Ethics 18 at 21.
127. Somerville, "Retrospective Overview," *supra* note 107 at 61.

should be more carefully examined. The ethics of the situation should be informed, but not clouded, by the humanitarian benefits of the potentially life-saving nature of xenotransplantation. Indeed, it seems that it would be equally true in Canada and internationally that, "given the pessimism about the prospects for containment of any new infection, the precautionary principle would appear to require that the proposed moratorium on xenotransplantation procedures [in England] be made indefinite."[128] While the Canadian National Forum had recommended that the public be consulted and the result was the recommendation for a moratorium on xenotransplantation, the precautionary principle would further dictate a more stringent delay or moratorium. The Canadian government does not appear willing to comply with the recommendations, and instead seems intent on following the United States approach of conducting clinical trials in order to assess the risks of xenotransplantation.

Furthermore, it seems to be problematic that the "precautionary principle" has been interpreted in different ways across jurisdictions; this may reflect the purposes and intentions of the interest groups of a particular jurisdiction. In October 2000, Health Canada, the Organisation for Economic Co-operation and Development (OECD) and the World Health Organization (WHO) jointly sponsored a Consultation on Xenotransplantation Surveillance.[129] The level of involvement of Health Canada is notable. In the *OECD Consultation Report*, the differing uses of the precautionary principle were raised as a problem in establishing harmonized standards:

> The Consultation reviewed how many countries are currently trying to address the potential risks and benefits of xenotransplantation, as well as their plans for specific policies, regulations, guidelines, standards and uses of national expert advisory bodies.... A common concern was the potential introduction of xenogeneic pathogens into a community, and in particular the uncertainty of predicting such an occurrence. *Thus, current national frameworks have incorporated very high benchmarks for safety—some countries have initiated moratoria, some have limited xenotransplantation to laboratory-based research, others to clinical trials only.*
>
> Most countries cited the "Precautionary Principle" as the basis for their action, but different meanings have been applied to this "principle," a fact that is having a profound influence on the approaches taken. In its most basic form, the Consultation participants thought that the principle implies that one should not wait until a risk is confirmed before taking action. *Thus, in light of the number of xenotransplantation clinical trials currently under way, a proactive engagement is recommended.*[130]

The Consultation concluded that international surveillance of xenotransplantation activities is required with a consensus as to minimal reporting requirements

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128. *Supra* note 126 at 22.

129. OECD, *OECD/WHO Consultation on Xenotransplantation Surveillance: Summary Report* (26 October 2001), <http://www.olis.oecd.org/olis/2001doc.nsf/LinkTo/dsti-stp-bio(2001)11-FINAL> [*OECD Consultation Report*].

130. *Ibid.* at 35 [italics in original document].

and processes. Indeed, the overall approach of the OECD seems to be to safeguard the development of cautious xenotransplantation clinical trials rather than to interpret the precautionary principle as I have done above. Thus, in the survey of current national xenotransplantation activities, it is noted that, "[i]t seems that xenotransplantation technology is on the way in … [t]here is no clear call for a total ban or moratorium."[131]

With respect to Health Canada's approach to the precautionary principle, the definition of minimizing risk and erring on the side of restraint has been modified. Thus, we see in the response to the question "What is Health Canada's interpretation of 'reasonable doubt' and the precautionary principle?" an answer that seems suited to the purposes of industry stakeholders:

> Since the precautionary [principle] was developed in international environmental law, it requires adaptation in the medical field. In medical terms, it is important to evaluate the risk of doing nothing versus the potential benefits. In medicine, it is necessary to balance theoretical risks with known risks. The result is a "balanced risk reduction" approach that is extrapolated from the environmental example. Examples of application of the precautionary principle to theoretical risks include blood products and new variant Creutzfeldt Jacob Disease.[132]

This method of unilaterally redefining international environmental standards is problematic. Indeed, it reflects the reservations voiced by the OECD above.

4.3. Xenotransplantation and Industry in Canada

> *Some such things have been hit upon in the last resort of surgery; most of the kindred evidence that will recur to your mind has been demonstrated, as it were, by accident—by tyrants, by criminals, by the breeders of horses and dogs, by all kinds of untrained clumsy-handed men working for their own immediate ends.*[133]

In considering the rationale for the Canadian government's enthusiasm for xenotransplantation, Industry Canada's treatment of xenotransplantation is enlightening. A study commissioned by Industry Canada and published on the Strategis website indicates:

> [a]n accelerating pace of discovery has affirmed biotechnology's scientific potential and scope. However, the industry's financial viability continues to face challenges…. To ensure continued development in biotechnology, inventors of successful products will need to be rewarded sufficiently to provide the incentives to continue discovering new therapies.[134]

Other Canadian government publications have emphasized the profit from the

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131. OECD, "Taking Preventative Action," <http://www1.oecd.org/publications/oberver/213/Article6_eng.htm>.
132. Health Canada, *Planning Workshop Report*, *supra* note 60.
133. Wells, *supra* note 1 at 135.
134. James J. Heller Consulting Inc., *Background Economic Study of the Canadian Biotechnology Industry* (Submitted to Industry Canada and Environment Canada, June 1995), <http://strategis.ic.gc.ca/pics/ip/helleref.pdf> at 109.

emerging biotechnology, and cast ethical concerns and risks instead as "hurdles" to be overcome. Some publications that had demonstrated such an emphasis on the profitability of xenotransplantation have since been removed from the Industry Canada websites, but the comments that had been published are still worth examination and scrutiny.

For instance, while it is no longer available online, the *Xenotransplantation Overview* that had been published in October 2000 by the Life Sciences Branch of Industry Canada explained the technology, the challenges of the procedure in overcoming rejection and the concern that transplant organs be pathogen free, but provided a disclaimer:

> It should be noted that at the time this overview was composed, organ xenotransplantation was an experimental technology. The most advanced attempts were experiments involving the transplantation of organs between different animal species; no clinical trials involving humans had been performed.[135]

Of course, we already know that xenotransplantation "experiments" have been conducted in much earlier clinical trials, though such a qualification is not supplied. While there is reference to the risk of infection, it is described as a phenomenon that "could be possible" and it is presented in such a way that implies that continued research would minimize the risk, as though research can control the unquantifiable and the unknowable. The ethical issues regarding xenotransplantation are not discussed, a link that had appeared at the bottom of the page read, "[f]or an overview of some of the ethical considerations associated with xenotransplantation and how industry and governments are addressing them please visit *Biotechnology: Ethics and the Industry*."[136] That target site has also been removed.

While it has since been removed from Industry Canada's Strategis website, or seems otherwise unavailable for online consultation, the page "Xenotransplantation Discussion Scenario" had appeared under the heading *Biotechnology: Ethics and the Industry*. This site had surveyed the broad ethical problems raised by xenotransplantation, but situated them as manageable. Thus, the National Forum's recommendation about seeking the public's approval of xenotransplantation is instead framed as a problem regarding the informed consent of society:

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135. Industry Canada, Life Sciences Branch, *Xenotransplantation Overview*, *supra* note 13. Indeed, the situation now appears to have changed, according to a study prepared for the Canadian Biotechnology Advisory Committee's "Project Steering Committee on Intellectual Property and the Patenting of Higher Life Forms" stated that "it is estimated that about 207 pigs were used in xenotransplantation associated studies in 1998 in Canada, while none were reported in the previous year," Clément Gauthier & Gilly Griffin, *The Use of Animals in Scientific Research and as Sources of Bioengineered Products* (March 2000), Canadian Biotechnology Advisory Committee <http://cbac-cccb.ca/epic/internet/incbac-cccb.nsf/vwapj/AnimalResearch_Gauthier_Griffin_e.pdf/$FILE/AnimalResearch_Gauthier_Griffin_e.pdf> at 21.

136. *Ibid.*

> How could such [societal] consent be obtained? One suggestion might be the active involvement of the public in policy development with respect to xeno-transplantation, including determinations of what results in animal-to-animal xenotransplants are a prerequisite for human trials, etc.[137]

Involving the public in determining how a technology will proceed is very different from considering the possibility that the public may prefer a moratorium and, if so, that option should be available. Similarly, under the heading "Ethics of xenotransplantation," allotransplants are described as a "very successful treatment for severe organ failure"[138]—despite the reservations of scientists discussed above.[139] The website then announced:

> If xenotransplants were this successful, it could virtually eliminate the need for organ waiting lists. *And with an estimated market of 100,000 patients a year, this option could make a major contribution to job creation, economic growth, and profits for the companies that develop the technology.*[140]

It is only in the next paragraph that the brief overview of the ethical considerations appeared, beginning with the sombre transition: "But there are risks and ethical questions to be considered."[141] The Canadian government's public presentation of this type of information regarding xenotransplantation effectively undermined ethical and public-health concerns, and demonstrated the government's commitment to facilitating the development of the business of xenotransplantation in Canada.

The Canadian government thus seems committed to certain policy initiatives, but too often the *business* of xenotransplantation is left untreated or ignored in the analysis of the benefits of xenotransplantation. In determining the appropriate level of transparency and public involvement in the process of proceeding with xenotransplantation, the *Planning Workshop Report* of Health Canada's Therapeutic Products Programme brought up "business ethics" in passing and, indeed, raised significant questions:

> What is the relationship between corporations and the development of this technology? Many questions around business ethics: transparency; accountability; degree to which product under development drives the process versus medical need; what is a conflict of interest?[142]

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137. Industry Canada, "Discussion Scenario," *supra* note 32.

138. *Ibid.*

139. Tilney, *supra* note 36.

140. Industry Canada, "Discussion Scenario," *supra* note 32 [emphasis added]. While this reference is no longer on the Industry Canada internet site, it has been cited elsewhere; see *e.g.* the reference in the position piece at Focus on the Family (Canada) Association, *Cloning: Optional…Necessary…Inevitable?*, Focus on the Family Canada <http://www.fotf.ca/familyfacts/analysis/071501.html>:

> These transgenic animals could greatly reduce the demand for human donors which far exceeds supply. The Organization for Economic Co-Operation and Development (OECD) has pointed out the potential market that exists: more than 100,000 people in the US alone are waiting for organ transplants. In this country, Industry Canada notes the job creation that would follow a boom in the availability of organs.

141. "Discussion Scenario," *ibid.*

142. *Supra* note 60 at 14.

Unfortunately, the group members charged with these questions were "unable to address the question of business ethics in the time available":

> In conclusion, it was stated that this is a confusing, far-reaching subject. The group came away with as many impressions of what was being asked as there were people in the room, leading participants to agree that public consultation would depend on an ability to present the issues to the public in a far more succinct way.[143]

Nevertheless, the relationship between government with industry and the potential pressure to proceed with clinical trials are rarely raised in the context of the presentation of interests in the debate. Instead, industry stakeholders often present themselves as being on the side of the debate advocating clinical trials due to the tragic organ shortage rather than due to the potential revenues that may come from a successful market in xeno-products, which, quite understandably, may have less currency with the public. Indeed, the *Public Consultation Report* rated "Corporate interests (*e.g.* pharmaceutical industry)" as the lowest in response to the question: "How much influence should each of the following have in the decision about proceeding with xenotransplantation?"[144] The Canadian government thus appears to be more committed to facilitating industry interests than to giving regard to the Canadian public's concerns—especially given the fact that, even though the first recommendation of the *Public Consultation Report* was a moratorium, this does not appear on the Canadian government's Fact Sheet regarding xenotransplantation.

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CONCLUSION

> *But I did not mean to die, and an incident occurred that warned me unmistakably of the folly of letting the days pass so—for each fresh day was fraught with increasing danger from the Beast Monsters.*[145]

THE IMPLEMENTATION OF STANDARDS in Canada for xenotransplantation represents an approach that is facilitative of this possibly risky biotechnology, rather than the cautious approach recommended by the National Forum and the *Public Consultation Report*. Neither the public statements of Health Canada nor its *Proposed Canadian Standard* demonstrates that this recommendation is being followed. Instead, as discussed above, while the public is "invited to participate" and its input is "deemed essential," the Canadian government seems committed to making xenotransplantation a reality, notwithstanding the moratorium recommendation of the *Public Consultation Report*. Nevertheless, should the Canadian government proceed with clinical trials, such trials ought to be conducted with effective and explicit regulatory controls on the development and experimentation with xenotransplantation in order to limit and curtail the risks of xenozoonosis.

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143. *Ibid.*
144. *Supra* note 62 at 23.
145. Wells, *supra* note 1 at 199.

The *Proposed Canadian Standard* facilitates the approval of clinical testing in Canada to allow research to be conducted here that may be prohibited in other jurisdictions. Furthermore, the revenues that Canada would generate as a result of such biotechnological development provide a motivation for the government to be less exacting than other nations. Less stringent regulations make Canada an attractive jurisdiction for biotechnology companies to do their business. Should this situation continue, it would seem to be incommensurate with international agreements on world health that require that the precautionary principle be respected. The primary motivating factor should be concern for patients and public health. While xenotransplantation may one day be beneficial for patients, until that time stringent regulation, requirements and safety standards—at least as demanding as those of other countries—ought to be set in place. The *Proposed Canadian Standard* represents only a partial move on the part of the Canadian government with respect to the regulation and control of the risks posed by xenotransplantation.

APPENDIX 1:

Recommendations of the Public Consultation on Xenotransplantation

1. That Canada not proceed with xenotransplantation involving humans at this time as there are critical issues that first need to be resolved.

2. That alternatives to xenotransplantation, such as prevention, expanding the human donor pool, mechanical substitutes, and stem cell research be further explored.

3. That the Canadian public receive more information about organ and tissue donation, healthy lifestyles, disease prevention, and disease management.

4. That pre-clinical research continue in order to gain further knowledge about the potential health risks and viability of xenotransplantation.

5. That stringent and transparent legislation and regulations be developed to cover all aspects of xenotransplantation clinical trials.

6. That the public continue to be informed and involved in discussions about the future of xenotransplantation.

7. That the citizen forum model be strongly considered for future consultations on complex and not widely understood policy issues.

APPENDIX 2:

Recommendations of the National Forum on Xenotransplantation

1. *Immunology:* Transplantation of solid, vascularized organs is still premature and requires significant pre-clinical research before clinical trials proceed. Some participants claimed that well designed and controlled clinical trials were the best strategy for advancing the development of successful xenotransplantation practices. Others believed that outstanding issues regarding immunological and infectious disease risks (*e.g.* retrovirus infection of human cells) were too numerous to sanction clinical trials at the present time. Preclinical research should be conducted in Canada. Pigs will likely provide the most acceptable source of organs and tissues.

2. *Xenozoonosis:* We need to develop and validate diagnostic methods for the detection of PERVs, and other potential human pathogens (derived from animal sources), so that we can better assess the infectious disease risks of xenotransplantation. Regulators and the National Advisory Committee need to examine the screening results for infectious agents in past or on-going clinical trials of xenotransplantation which are occurring outside of Canada. Summaries of their conclusions should be made public as part of the public consultation process prior to deciding whether or not xenotransplantation clinical trials will occur in Canada. While genetic modification of donor animals appears to be necessary to prevent rejection of solid organs, it would be important to evaluate these changes in terms of the augmentation of infectious disease risks.

3. *Use and Care of Animals:* The use of animals for food or in medical research does not automatically justify their use for xenotransplantation. The Canadian public should decide whether animals ought to be used as sources of donor organs and tissues for humans. Whatever Canadians decide, animals should only be considered for xenotransplantation if other therapies are not available. Medical science should minimize the number of animals used for this purpose by improving existing systems for collecting and distributing human organs and preventing disease; coordinating human surgeries to ensure that the greatest number of tissues and organs from a single animal are put to good use, though sequential surgical harvesting should not be allowed; high level of biosecurity for xenotransplantation source animals will be necessary to maintain pathogen-free herds; animals must be carefully monitored for the development of disease; animals must be raised in a manner that respects their social and behavioural needs; Health Canada should be the regulatory body for appropriate care and use of animals for xenotransplantation. International harmonization for animal care in regulations or standards is recommended. An international registry should be established to avoid duplication in the creation of "transgenic" or genetically altered" animal strains.

4. *Patient Ethics:* The risk of xenozoonotic disease transmission means that patients receiving transplanted animal tissue would need to be closely monitored for the rest of their lives. Information on their medical condition would have to be fed into databanks so that doctors and scientists could learn from each transplant procedure. Moreover, since xenozoonotic diseases could spread among humans, the patient's close contacts would need to be monitored as well.

5. *Surveillance and Patient Registries:* Patients may need to be selected for clinical trials based on the likelihood that they would consent to lifelong monitoring of their health status, as well as an autopsy after their death. Comprehensive monitoring could limit a patient's autonomy and privacy; the risk of xenozoonotic disease transmission means the patient's close contacts may need to be monitored too; informed consent to participate in clinical trials would therefore have to be obtained from patients as well as close contacts. Whether for clinical trials or the active practice of xenotransplantation, national databases would have to be created to manage all of the relevant information. HPB, industry, and scientific community should work with other nations to develop common principles for xenotransplantation. Cost/benefits analysis and clinical introduction of these new technologies should be consistent with the measures applied to the adaptation and introduction of other medical procedures.

6. *Clinical Trials:* The Forum proposed that Health Canada regulate xenografts just like any other therapeutic products under the *Food and Drugs Act*. This means that clinical trials involving xenografts would first have to be approved by the federal regulator. In addition, the regulator would apply a "standards-based" approach, which would give rules governing xenotransplantation the force of law. Standards-based regulation means that every practice associated with xenotransplantation would have to meet or exceed clearly defined standards under federal law. For example, standards could define how animals should be raised, how tissues must be handled, how surgeons are to be accredited and what information must be registered in a databank. An advantage of this approach is that it is easier to update standards than to keep amending regulations.

7. *Ethics Review Boards:* Hospitals or other research establishments that wanted to conduct clinical trials on xenotransplantation would have to obtain approval from their internal Research Ethical Boards, as is done for all types of clinical trial proposals. This approval would be in addition to the approval of the federal regulator mentioned above. Among other things, the Boards would have to ensure that patients and their contacts were fully informed and counseled before giving their consent to participate in clinical trials. The Forum called for the creation of a National Advisory Board on Xenotransplantation—a panel of independent

experts that would advise both the regulator and the local Research Ethics Boards. A proposed National Animal Care Committee would also provide guidance on the ethical use and care of animals.

8. *Standards and Screening:* In addition to the National Advisory Board on Xenotransplantation and the National Animal Care Committee, the Forum suggested that a complete regulatory model would be inappropriate and that it would be a very labour intensive to initiate change. Because of the current lack of knowledge that exists in this field, it was agreed that the approach must be flexible. Voluntary guidelines were ruled out, as this approach did not have enough "teeth" to verify compliance. A fluid standards based regulatory approach was thought to be best. With respect to monitoring, intense screening at the time of transplantation, and this level of observation should probably continue for 12 to 24 months. Beyond that time period, active screening (surveillance) should continue, but it would tend to be less frequent. It was felt that a "common sense approach" be applied—but that screening, of some sort, should be life long.