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## The Development of Regulatory Standards for Gene Therapy in the European Union

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# The Development of Regulatory Standards for Gene Therapy in the European Union

Charles F. De Jager

## **Abstract**

This note examines the EU's efforts to regulate gene therapy, considering the Union's resolve to establish scientifically, economically, and morally sound parameters acceptable to its varied constituency. This includes discussion of legal and ethical considerations, biotechnology goals in the EU, and EU-wide uniform regulations.

# THE DEVELOPMENT OF REGULATORY STANDARDS FOR GENE THERAPY IN THE EUROPEAN UNION

Charles F. De Jager\*

## INTRODUCTION

In the more than forty years since James Watson and Francis Crick discovered the structure of Deoxyribonucleic Acid<sup>1</sup> ("DNA") in 1953,<sup>2</sup> researchers have made formidable advances in molecular genetics.<sup>3</sup> Scientists have accumulated enough knowledge to begin to apply in human subjects the techniques of genetic manipulation<sup>4</sup> developed in animal trials.<sup>5</sup> This transition has opened a new field of research that is at once promis-

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\* J.D. Candidate, 1996, Fordham University. The 1994 MCI-Fordham International Law Fellowship generously funded the research for this Note. The Author would like to thank Ms. Isabelle Arnal, Secretary, European Union Ethical Committee on Biotechnology.

1. JAMES D. WATSON, *THE DOUBLE HELIX: A PERSONAL ACCOUNT OF THE DISCOVERY OF THE STRUCTURE OF DNA* (1968) [hereinafter *WATSON, THE DOUBLE HELIX*]; James D. Watson & Francis Crick, *Genetical Implications of the Structure of Deoxyribonucleic Acid*, 171 *NATURE* 964 (1953). Deoxyribonucleic Acid is a type of nucleic acid found principally in the nuclei of animal and vegetable cells that is considered to be the repository of hereditary characteristics. *Id.*

2. See WATSON, *THE DOUBLE HELIX*, *supra* note 1 (including basic scientific background).

3. Louis J. Elsas II, *A Clinical Approach to Legal and Ethical Problems in Human Genetics*, 39 *EMORY L.J.* 811, 812 (1990) [hereinafter *Clinical Approach*]; see JAMES D. WATSON ET AL., *RECOMBINANT DNA* (2d ed. 1992) [hereinafter *RECOMBINANT DNA*] (describing advances in genetic research).

Even though genetic counseling and prenatal diagnosis are invaluable for families who are known to have an inherited disorder, there exists a long-cherished hope that patients already afflicted might be treated by replacing their defective gene with the normal gene. For many years this project seemed to be very remote, more aptly belonging to the realms of science fiction. Only with the application of recombinant DNA techniques to human genetic diseases did research to develop practicable methods of gene therapy become possible.

*Id.* at 567.

4. David A. Kessler et al., *Regulation of Somatic-Cell Therapy and Gene Therapy by the Food and Drug Administration*, 329 *NEW ENG. J. MED.* 1169 (1993) [hereinafter *Kessler, Regulation*].

5. See *id.* at 1171 (discussing testing in animals in investigational phases of gene therapy); John C. Fletcher, *Moral Problems and Ethical Issues in Prospective Human Gene Therapy*, 69 *VA. L. REV.* 515, 528-29 (1983) [hereinafter *Fletcher, Moral Problems*] (discussing widely-accepted practice of experimentation on animals to assess risks and benefits of experimentation on humans).

ing and controversial: gene therapy.<sup>6</sup> Gene therapy involves the manipulation of genetic material to diagnose, prevent, or treat disease.<sup>7</sup> Through the efforts of researchers around the world, scientific advances in the past decade have made clinical testing of gene therapy a reality.<sup>8</sup> This new technology further allows the rapid development of products for a variety of applications, including use as vaccines,<sup>9</sup> diagnostic agents,<sup>10</sup> drug-delivery systems,<sup>11</sup> and treatment for malignant, infectious, and genetic diseases.<sup>12</sup> Various approaches, at different stages of testing, are being investigated to treat cystic fibrosis, atherosclerosis, hemophilia, cancer, and chronic infections such as Human Immunodeficiency Virus ("HIV").<sup>13</sup>

Gene therapy, while having tremendous medical and economic potential, is also controversial.<sup>14</sup> Public resistance to gene therapy can be great given real or perceived possibilities for abuse or harm inherent in this technology.<sup>15</sup> The concept of genetic manipulation also conflicts with certain national and cultural norms.<sup>16</sup> Thus, individual nations in which gene therapy research is conducted have realized the need to regulate the

6. GROUP OF ADVISERS ON ETHICAL IMPLICATIONS OF BIOTECHNOLOGY OF THE EUROPEAN COMMISSION, REPORT ON ETHICAL ASPECTS OF GENE THERAPY 1 (1994) [hereinafter ARCHER REPORT]. "Human gene therapy is the deliberate transfer of genetic material into a patient's cells with the purpose of curing or preventing a disease." *Id.*; see DEP'T OF HEALTH AND HUMAN SERVICES, MEMORANDUM (1991). "Gene therapy is a medical intervention based on modification of the genetic material of living cells." *Id.* at 3.

7. Kessler, *Regulation*, *supra* note 4, at 1169; see ARCHER REPORT, *supra* note 6, at 1 (defining gene therapy).

8. W. French Anderson, *Human Gene Therapy*, 256 SCI. 808, 809 (1992) [hereinafter *Human GT*]. "Human gene therapy has progressed from speculation to reality in a short time." *Id.*

9. Kessler, *Regulation*, *supra* note 4, at 1169. Vaccines are any preparation intended for active immunological prophylaxis. *Id.*

10. *See id.* Diagnostic agents are devices or techniques used to determine the nature of a disease. *Id.*

11. *See id.* Drug-delivery systems are means or techniques devised to distribute therapeutic agents. *Id.*

12. *See id.* Examples of these types of diseases are, respectively, cancer, Human Immunodeficiency Virus ("HIV"), and hemophilia. *Id.*

13. *Id.*

14. RECOMBINANT DNA, *supra* note 3, at 569; see *Human GT*, *supra* note 8, at 812 (discussing promise and controversy inherent in gene therapy).

15. LeRoy Walters, *The Ethics of Human Gene Therapy*, 320 NATURE 225 (1986) [hereinafter *Ethics*].

16. *Id.*

field.<sup>17</sup> The European Union ("Union" or "EU"),<sup>18</sup> however, has not enacted specific legislation regulating gene therapy research.<sup>19</sup> As in other leading technological fields, the success of the Union in gene therapy depends upon its ability to harmonize its research efforts.<sup>20</sup> The Union, therefore, must balance these concerns in elaborating gene therapy regulations, while also trying to remain competitive globally.

This Note examines the European Union's efforts to regulate gene therapy, considering the Union's resolve to establish scientifically, economically, and morally sound parameters acceptable to its varied constituency. Part I provides the scientific background on gene therapy, examines the legal and ethical issues that gene therapy raises, and considers current regulatory frameworks. Part II examines the goals of the European Commission in biotechnology as set out in *Growth, Competitiveness, Employment: The Challenges and Ways Forward Into the 21st Century, White Paper*<sup>21</sup> ("White Paper") and the recommendations of the Group of Advisers on the Ethical Implications of Biotechnology presented in the *Report on Ethical Aspects of Gene Therapy*<sup>22</sup> ("Archer Report"). Part III stresses the importance of Union-wide regula-

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17. Alexander Morgan Capron, *Which Ills to Bear?: Reevaluating the "Threat" of Modern Genetics*, 39 EMORY L.J. 665, 671 (1990) [hereinafter Capron, "Threat"].

18. See Treaty Establishing the European Community, Feb. 7, 1992, [1992] 1 C.M.L.R. 573 [hereinafter EC Treaty], *incorporating changes made by* Treaty on European Union, Feb. 7, 1992, O.J. C 224/1 (1992), [1992] 1 C.M.L.R. 719, 31 I.L.M. 247 [hereinafter TEU]. The TEU, *supra*, amended the Treaty Establishing the European Economic Community, Mar. 25, 1957, 298 U.N.T.S. 11, 1973 Gr. Brit. T.S. No. 1 (Cmd. 5179-II) [hereinafter EEC Treaty], *as amended by* Single European Act, O.J. L 169/1 (1987), [1987] 2 C.M.L.R. 741 [hereinafter SEA], in TREATIES ESTABLISHING THE EUROPEAN COMMUNITIES (EC Off'l Pub. Off. 1987). Until 1995, the twelve EU Member States were Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, and the United Kingdom. TEU, *supra*, pmbl. On January 1, 1995, Austria, Finland, and Sweden became Member States of the European Union. See Hugh Carnegie, *Sweden Gives Clear Yes to EU: Vote in Favour of Membership Keeps Enlargement Timetable on Course*, FIN. TIMES, Nov. 14, 1994, at 1 (discussing accession of new states). The enlarged Union does not include Norway, which rejected membership in the Union in November 1994. John Darton, *Vote in Norway Blocks Joining Europe's Union*, N.Y. TIMES, Nov. 29, 1994, at A1.

19. ARCHER REPORT, *supra* note 6, at 8.

20. See BERMAN ET AL., CASES AND MATERIALS ON EUROPEAN COMMUNITY LAW (1992) [hereinafter EC Law].

21. Commission of the European Communities, *Growth, Competitiveness, Employment: The Challenges and Ways Forward Into the 21st Century, White Paper*, COM (93) 700 Final (1993) [hereinafter White Paper].

22. ARCHER REPORT, *supra* note 6.

tion of research and clinical efforts in gene therapy and warns that lest the Union fully carry out its goals of coordination and harmonization,<sup>23</sup> it will be putting itself at a competitive disadvantage in the field of gene therapy. This Note concludes that the Union will jeopardize its chances of exploiting the full potential of a promising new technology should it fail to articulate uniform gene therapy regulations.

### I. APPLICATIONS AND IMPLICATIONS OF GENE THERAPY: AN OVERVIEW

Modern advances in biotechnology have allowed scientists to develop protocols<sup>24</sup> to treat genetic diseases in humans by replacing defective genes with functional ones through gene therapy.<sup>25</sup> Thus, the results of gene therapy research have yielded medical applications that are presently being used.<sup>26</sup> Given the potential for abuse inherent in the technology, however, the legal and ethical issues raised by the field of gene therapy are as great as its promise.<sup>27</sup> A delicate balance must therefore be struck between the progress of scientists and the management of risks.<sup>28</sup> Current regulatory frameworks at different levels within the European Union manage various aspects of gene therapy research.<sup>29</sup>

#### A. Gene Therapy

Both germline gene therapy<sup>30</sup> and somatic gene therapy<sup>31</sup>

23. See EC LAW, *supra* note 20, at 428. "The success of the Community depends in large part on its ability to harmonize Member State laws." *Id.*

24. Kessler, *Regulation*, *supra* note 4, at 1171-72. A protocol is a precise and detailed plan for the study of a biomedical problem or for a regimen of therapy. *Id.*

25. Theodore Friedmann, *Progress Toward Human Gene Therapy*, 244 SCI. 1275 (1989) [hereinafter *Progress*]. "[B]ased on the assumption that definitive treatment for genetic diseases should be possible by directing treatment to the site of the defect itself — the mutant gene —" gene therapy is extremely promising scientifically. *Id.*

26. *Human GT*, *supra* note 8, at 809.

27. *Progress*, *supra* note 25, at 1275 (supporting proposition that gene therapy is simultaneously promising and controversial).

28. Judith Areen, *Regulating Human Gene Therapy*, 88 W. VA. L. REV. 153, 170 (1985) [hereinafter Areen, *Regulating Human GT*].

29. ARCHER REPORT, *supra* note 6, at 7.

30. See RECOMBINANT DNA, *supra* note 3, at 569 (describing germline gene therapy as targeting germline cells: gametes, zygotes, and early embryos (4-8 cells)).

31. See *id.* (describing somatic gene therapy as targeting somatic cells (all other cells besides germline cells)).

encompass interventions in which one or more genes<sup>32</sup> are introduced within the cells of organisms to treat, diagnose, or prevent diseases linked to genetic anomalies.<sup>33</sup> These genetic defects are the result of a mutation.<sup>34</sup> A mutation causes the protein derived from such gene either to be absent or to have its activity altered, affecting the functions of certain or all other cell types in the body.<sup>35</sup> These changes in cellular activity eventually affect organ functions, generating clinical symptoms that medical doctors may observe.<sup>36</sup> The introduction of a functional gene<sup>37</sup> into a cell<sup>38</sup> may correct cellular imbalances<sup>39</sup> resulting from missing or altered biochemical activity.<sup>40</sup> The aim of gene therapy, therefore, is to eliminate the clinical symptoms by attacking problems at their root.<sup>41</sup>

### 1. Somatic and Germline Gene Therapy Distinguished

Two kinds of gene therapy are generally distinguished:

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32. See RECOMBINANT DNA, *supra* note 3, at 6-7. A gene is a functional unit of heredity that occupies a specific place or locus on a chromosome, is capable of reproducing itself exactly at each cell division, and is capable of directing the formation of an enzyme or other protein. *Id.*

33. ARCHER REPORT, *supra* note 6, at 1; see STOA, BIOETHICS IN EUROPE 80 (1992) [hereinafter BIOETHICS IN EUROPE]. "Gene therapy entails inserting a gene, a DNA fragment, into the cells of an organism in order to treat some pathological condition based on a genetic defect." *Id.*

34. See RECOMBINANT DNA, *supra* note 3, at 34. A mutation is a change in the character of a gene that is perpetuated in subsequent divisions of the cell in which it occurs. *Id.*

35. Julie L. Gage, *Government Regulation of Human Gene Therapy*, 27 JURIMETRICS J. 200 (1987) [hereinafter Gage, *Government Regulation*].

36. *Id.*

37. Thomas O. McGarity & Sidney A. Shapiro, *Public Regulation of Recombinant DNA Gene Therapy*, 3 J. LEGAL MED. 185, 187-88 (1982) [hereinafter McGarity & Shapiro]; see RECOMBINANT DNA, *supra* note 3, at 569 (describing replacement of mutant genes by normal genes).

38. *Progress*, *supra* note 25, at 1276-80. Many techniques, mechanical, physical, chemical, biological, are used to introduce foreign DNA into the target cells. *Id.* Insertion techniques include: virus or retrovirus vectors, direct microinjection into the cell nucleus, electroporation, precipitation by chemical agents, fusion with liposomes, and shooting with tungsten microprojectiles coated with DNA. *Id.*

39. Gage, *Government Regulation*, *supra* note 35, at 200.

40. *Id.*

41. BIOETHICS IN EUROPE, *supra* note 33, at 80. "Recessive mutations can be more readily treated. . . . In this instance, inserting into 'ill' cells a single copy of the normal gene is enough to restore the function. Recently, the scope of gene therapy has been expanded from simple correction of mutations to cover treatment of pathological traits." *Id.*

germline and somatic gene therapy.<sup>42</sup> The distinction is made on the basis of the targeted cell type, either germline cells or somatic cells.<sup>43</sup> Germline cells are gametes,<sup>44</sup> zygotes,<sup>45</sup> and the undifferentiated cells of embryos in the early stages of development.<sup>46</sup> All of these cells have the potential to contribute genetic material to offspring.<sup>47</sup> Somatic cells, the remaining cells of the organism, do not have this potential.<sup>48</sup> In somatic gene therapy the genetic changes introduced are not transmitted to the progeny, while they would be in the case of germline gene therapy.<sup>49</sup>

Because of this potential for the transmission of genetic alterations in perpetuity, germline gene therapy is much more controversial than somatic gene therapy.<sup>50</sup> By targeting germi-

42. RECOMBINANT DNA, *supra* note 3, at 569 (describing distinction drawn between genetic manipulations involving somatic cells and genetic manipulations involving germline cells).

43. *Id.*

44. See Gage, *Government Regulation*, *supra* note 35, at 201. Gametes are the sex cells that contain the genetic information to be transmitted to the offspring. *Id.* Spermatozoa are the male gametes. *Id.* Ova are the female gametes. *Id.*

45. See *id.* Zygotes are fertilized eggs. *Id.*

46. *Id.*

47. RECOMBINANT DNA, *supra* note 3, at 569 (stating that changes resulting from germline gene therapy would be passed on to subject's progeny).

48. *Id.* "The outcome [of somatic gene therapy] is a genetic alteration that is restricted to the treated patient . . ." *Id.*

49. *Id.* Somatic cell gene therapy eliminates or reduces molecular defects in somatic cells, affecting only the individual. *Id.* Germline gene therapy, however, corrects genetic defects in germline cells, affecting the individual and its offspring. *Id.*

50. *Id.*

Gene therapy involving germ line cells is more controversial, because the modification is passed on to the children of the treated patient. This is considered by some to be ethically unacceptable, because, it is argued, we do not have the right to impose such a change on our descendants, no matter how well intentioned our reasons.

*Id.*; see *Progress*, *supra* note 25, at 1280.

Deliberate or inadvertent modification of human germ line cells can presumably occur by many of the same methods described here. The potential role of germ line manipulation for the prevention of genetic disorders is far less clear than is somatic cell modification, and one response to the possibility of germ line genetic modification has been to suggest that it is so full of technical and ethical uncertainties that it should not be performed. However, it seems unwise and premature to take such a severe position, and it has been suggested that the need for efficient disease control or the need to prevent damage early in development or in inaccessible cells may eventually justify germ line therapy. This most problematical of all issues in gene therapy requires much more examination.

*Id.*

nal cells or embryos, germline gene therapy attempts to eradicate the anomaly permanently from the patrimony of future generations, as well as the individual in the case of embryos.<sup>51</sup> Currently, however, the results of germline gene therapy are highly unpredictable.<sup>52</sup> Although there have been trials in animals, germline gene therapy has not been performed on humans to date.<sup>53</sup> Thus, it is not yet available in a clinically useful form.<sup>54</sup>

Somatic gene therapy, on the other hand, does not involve changes that affect the patrimony of future generations.<sup>55</sup> As a result, both technically and ethically, somatic gene therapy is not much different from other high-technology therapeutic interventions such as organ or bone marrow transplantations.<sup>56</sup> As with other experimental therapeutic techniques, traditional guidelines must be observed.<sup>57</sup> These guidelines include exten-

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51. BIOETHICS IN EUROPE, *supra* note 33, at 84.

52. *Id.* at 80. "Current practices involve [both] a high cell lethality (transgenic animal embryos able to develop normally account for no more than 2-3%) and risks linked to random insertion of foreign DNA that may give rise to mutations detrimental to the functionality of the genome." *Id.*; see *Human GT*, *supra* note 8, at 812.

The feeling of many observers is that germline gene therapy should not be considered until much more is learned from somatic cell gene therapy, until animal studies demonstrate the safety and reliability of any proposed procedure, and until the public has been educated as to the implications of the procedure.

*Id.*

53. RECOMBINANT DNA, *supra* note 3, at 571 (describing germline gene therapy experiment in animals); see BIOETHICS IN EUROPE, *supra* note 33, at 80. "In animals, exogenous DNA is usually inserted into 1) gametes 2) in vitro fertilised zygotes (the first cells obtained by gamete fusion) or 3) into totipotent embryonic cells (cells of embryos at the early developmental stages)." *Id.*

54. ARCHER REPORT, *supra* note 6, at 1.

55. RECOMBINANT DNA, *supra* note 3, at 569.

56. *Id.* Somatic gene therapy "is analogous to the treatment of genetic disorders by organ or tissue transplantation." *Id.*; BIOETHICS IN EUROPE, *supra* note 33, at 83. Somatic cell gene therapy is intended as a therapy for genetic diseases by replacing the defective genetic material at the core of the disease with functioning genetic material. *Id.*; *Human GT*, *supra* note 8, at 813. Gene therapy procedures currently involve three basic steps: removal of proliferous cells from the patient; insertion of the desired gene into in vitro cultured cells; and return of the genetically modified cells back into the patient. *Id.*; BIOETHICS IN EUROPE, *supra* note 33, at 80-81. Such a procedure confines the applicability of somatic gene therapy to disorders: linked to a recessive genetic trait; involved with a constitutive expression without implying any complex regulation mechanism; affecting proliferous tissues thus allowing in vitro culture of cells (blood cells, endothelial cells, fibroblasts, hepatic cells); and affecting functions that can be restored even with a low rate of "corrected" cells. *Id.*

57. WORLD MEDICAL ASSOCIATION, DECLARATION OF HELSINKI (revised 1989) [hereinafter HELSINKI DECLARATION]; GOOD CLINICAL PRACTICE FOR TRIALS ON MEDICINAL

sive in vitro and animal experimentation<sup>58</sup> and attentive consideration of the costs and risks associated with the transition to experimentation in humans.<sup>59</sup> Currently, somatic gene therapy is being practiced on human subjects in the context of clinical trials in a growing number of clinical centers around the world, including several in European countries.<sup>60</sup>

## 2. Medical Applications of Gene Therapy

Many genetic disorders are considered treatable through somatic gene therapy.<sup>61</sup> Scientists believe that in the future they will also be able to treat more complex genetic traits and other kinds of disorders.<sup>62</sup> Various approaches, at different stages of testing, are being investigated to treat cystic fibrosis, atherosclerosis, hemophilia, cancer, and chronic infections such as HIV.<sup>63</sup> This new technology further allows the rapid tailoring of products for a variety of other applications, including use as vaccines, diagnostic agents, drug-delivery systems, and treatment of infec-

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PRODUCTS IN THE EUROPEAN COMMUNITY [hereinafter GOOD CLINICAL PRACTICE] (available from the Commission of the European Communities); NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, BELMONT REPORT (1975) [hereinafter BELMONT REPORT].

58. *Id.*

59. *Progress, supra* note 25, at 1280.

As is true with all other new procedures in medicine, therapeutic studies of gene therapy in human patients will be performed with imperfect knowledge when technical uncertainties and imperfections are outweighed by clinical needs. The balance between uncertain harm and desired benefits has been examined carefully by a number of religious, ethical, and public policy bodies . . . . All have agreed that somatic genetic manipulation for the purpose of ameliorating disease should be pursued.

*Id.* (citations omitted).

60. *Human GT, supra* note 8, at 809.

61. *BIOETHICS IN EUROPE, supra* note 33, at 81.

Disorders considered treatable through somatic cell gene therapy include: immunodeficiency syndrome resulting from adenosine deaminase deficiency (ADA); immunodeficiency syndrome resulting from a lack of enzyme purinonucleoside phosphorylase (PNP); a neurological syndrome resulting from a deficiency of enzyme hypoxanthine-guanine-phosphoribosyl-transferase (Lesch-Nyhan); cystic fibrosis (through direct DNA transfer); Duchenne muscular dystrophy; and haemophilia.

*Id.*

62. *Id.*; see *Ethics, supra* note 15, at 225 (stating that as of time article was written in 1986 only simplest kinds of genetic defects were considered viable candidates for gene therapy).

63. Kessler, *Regulation, supra* note 4, at 1169-70 (listing diseases being considered for gene therapy treatment).

tious diseases.<sup>64</sup>

After two unsuccessful attempts in the preceding twenty years,<sup>65</sup> a team of researchers from the National Institutes of Health<sup>66</sup> ("NIH") performed the first fully sanctioned and scientifically sound gene therapy intervention in humans in the United States in 1990.<sup>67</sup> An ever-increasing number of clinical trials have been approved and initiated since, especially in the United States.<sup>68</sup> Progress has been more gradual in Europe although most Member States have the requisite knowledge and technology to pursue gene therapy research.<sup>69</sup>

### B. *Legal and Ethical Issues Raised by Gene Therapy*

As medically promising as gene therapy may be, the possibilities for abuse inherent in the field are great.<sup>70</sup> As an experimental technology,<sup>71</sup> gene therapy also presents risks to its subjects that are not yet fully quantifiable.<sup>72</sup> Thus, gene therapy raises weighty legal and ethical issues.<sup>73</sup> Within a historical con-

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64. *Id.* (discussing gene therapy products and applications).

65. Fletcher, *Moral Problems*, *supra* note 5, at 524-28. Dr. Stanfield Rogers initiated the first somatic gene therapy trial in humans in 1970. *Id.* at 525. Rogers attempted unsuccessfully to treat patients affected by a neurological syndrome caused by a deficiency of the enzyme arginase by using Shope papilloma viruses. *Id.* This early experiment was followed in 1980 by that of Dr. Martin Cline. *Id.* at 527. Unlike Rogers, Cline acted in violation of scientific and ethical research standards for human subjects, attempting gene therapy for thalassaemia through bone marrow treatments. *Id.* at 527-28. Both attempts were scientifically premature and generally criticized. *Id.* at 524-25.

66. See Capron, "Threat", *supra* note 17, at 671 (describing generally function of National Institutes of Health ("NIH")). The NIH provides federal support and guidelines for gene therapy. *Id.*

67. BIOETHICS IN EUROPE, *supra* note 33, at 80. Ultimately, Blaese, Culver, and Anderson of the National Institutes of Health realized the first authorized gene therapy initiative in September 1990 in the United States. *Id.* at 80. The team transferred cells modified through the insertion of an ADA gene into a patient whose immune system was seriously endangered. *Id.*

68. *Id.*; see *Human GT*, *supra* note 8, at 809 (listing protocols initiated in United States as of May 1992, outnumbering protocols elsewhere around world by ratio of four to one).

69. *Human GT*, *supra* note 8, at 809. In Europe, the first human gene therapy protocol was initiated by an Italian group based at the Istituto San Raffaele in Milan in 1992. *Id.* at 811. Various efforts in other Member States of the European Union have followed. *Id.* at 809.

70. RECOMBINANT DNA, *supra* note 3, at 569.

71. BIOETHICS IN EUROPE, *supra* note 33, at 83.

72. *Id.*

73. See *supra* note 14 and accompanying text (discussing the promise and controversy inherent in gene therapy).

text, gene therapy raises the memory of the racist eugenics and racial hygiene experiments of Nazi Germany,<sup>74</sup> producing fears of enhancement genetic engineering.<sup>75</sup> Within moral and religious contexts, gene therapy raises concerns for the sanctity of life.<sup>76</sup>

Enhancement genetic engineering is closely related to gene therapy.<sup>77</sup> It utilizes the same technology and could be carried out on both somatic and germline cells.<sup>78</sup> At present, however, somatic gene therapy techniques are considered ethically admissible only for the treatment or prevention of serious diseases.<sup>79</sup> Should enhancement genetic engineering ever be deemed admissible, a more philosophical debate would have to be initiated

74. DANIEL KEVLES, *IN THE NAME OF EUGENICS: GENETICS AND THE USES OF HUMAN HEREDITY* (1985) [hereinafter KEVLES, *EUGENICS*]; BIOTETHICS IN EUROPE, *supra* note 33, at 89.

The hottest debate on this issue is probably in Germany where several public interest associations, organizations of handicapped persons and other groups have publicly expressed their concern for its potential association with positive eugenics. This is obviously linked to Germany's history and the connotation of the word 'eugenics' during the Nazi period. It is very important for the German public to discuss whether eugenic ideas are favored by the new biology and medicine because of Germany's history.

*Id.*

Generally, European public opinion is favourable towards SGT [somatic gene therapy] and does not waiver from the attitude of experts. The Eurobarometer 35.1 on Biotechnology shows that the great majority of the persons interviewed think that such research is worthwhile and should be encouraged. The major opposition to the application of genetic engineering in humans is in West Germany where 15.2% tend to disagree and 15% definitely disagree with such applications (9.4% and 10% are the European averages).

*Id.*

75. *Clinical Approach*, *supra* note 3, at 830.

76. *Id.* at 832.

77. *Human GT*, *supra* note 8, at 812. An example of enhancement genetic engineering is the transfer of a gene into cells of a healthy human being with the purpose of improving desired characteristics such as height. *Id.*

78. *Id.*

79. W. French Anderson, *Human Gene Therapy: Why Draw a Line?*, 14 J. MED. & PHIL. 681 (1989) [hereinafter *Why Draw a Line?*]. Serious diseases are diseases that cause significant suffering and premature death. *Id.* at 688. *Human GT*, *supra* note 8, at 812 (1992).

Correction of a genetic defect that causes serious illness is one thing, but to try to alter a characteristic such as size (by administration of a growth hormone gene to a normal child, for example) is quite another. This area is further clouded by major social implications as well as by the problem of how to define when a given gene is being used for treatment (or for preventing disease) and when it is being used for "enhancement."

*Id.*

in our society on the ethical implications of betterment of certain more trivial human traits.<sup>80</sup> The current consensus is that enhancement genetic engineering and its eugenic implications are inadmissible.<sup>81</sup> As sufficient knowledge and expertise to experiment with enhancement genetic engineering exist,<sup>82</sup> however, thorough control mechanisms must be in place to prevent any such deviations from legitimate gene therapy procedures.<sup>83</sup>

Many observers object to the potential effects of germline gene therapy, sustaining, on moral<sup>84</sup> or religious<sup>85</sup> grounds, the right of human beings to inherit an unaltered genetic blueprint.<sup>86</sup> Germline gene therapy is also controversial because it involves the manipulation of human embryos.<sup>87</sup> Germline gene therapy, however, could prove to be as promising as somatic gene therapy.<sup>88</sup> As the development and exploitation of germline gene therapy is eventually considered or actually permitted, therefore, it will have to be subject to close scrutiny and tight controls.

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80. ARCHER REPORT, *supra* note 6, at 1-2.

Consequently, enhancement genetic engineering is presently excluded from the ethically admissible clinical trials and, for that reason, will not be considered in this Report. If, in the future, clinical and ethical indications arise for gene therapy of minor diseases or even for certain health improvements, the matter should be discussed on a case by case basis.

*Id.*

81. *Id.*

82. *Human GT*, *supra* note 8, at 812.

83. *Ethics*, *supra* note 15, at 225.

84. Edward J. Larson, *Human Gene Therapy and the Law: An Introduction to the Literature*, 39 EMORY L.J. 855, 861-62 (1990) [hereinafter Larson, *Introduction*]; see Fletcher, *Moral Problems*, *supra* note 5, at 515 (discussing generally and defining moral and ethical issues).

85. See *Clinical Approach*, *supra* note 3, at 832-36 (discussing societal, personal, and religious issues surrounding germline gene therapy, including sanctity of life).

86. BIOETHICS IN EUROPE, *supra* note 33, at 84.

Many authors sustain that man - including future generations - is entitled to certain rights including the right to inherit a non-modified patrimony and the right of autonomy. Consequently, man should respect the patrimony and autonomy of future generations. For this reason alone some would like to see [germline gene therapy] prohibited. Others sustain that the human genome is sacred and therefore intangible calling for the ban of this technique.

*Id.*; see RECOMBINANT DNA, *supra* note 3, at 569 (presenting argument that changes may not be imposed on future generations).

87. ARCHER REPORT, *supra* note 6, at 10.

88. *Progress*, *supra* note 25, at 1280.

### C. *Current Regulatory Frameworks in the European Union*

Efforts at gene therapy regulation in the European Union have resulted in different approaches for germline gene therapy and somatic gene therapy.<sup>89</sup> While the former generally is currently considered to be too risky,<sup>90</sup> the latter is less controversial and in some ways akin to other high-technology therapies.<sup>91</sup> Certain aspects of somatic gene therapy, therefore, are subject either to broader existing EU biotechnology regulations<sup>92</sup> or to the controls of the European Medicines Evaluation Agency.<sup>93</sup> To date, however, gene therapy guidelines exist only at various levels within the individual Member States.<sup>94</sup> No comprehensive Union-wide regulation of gene therapy research has been articulated.<sup>95</sup>

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89. See *BIOETHICS IN EUROPE*, *supra* note 33, at 80-91 (discussing different treatment of each type of gene therapy).

90. *Human GT*, *supra* note 8, at 812.

91. *Id.*; see *BIOETHICS IN EUROPE*, *supra* note 33, at 87.

The Danish Council of Ethics, in its 1989 report on the protection of human gametes, fertilized ova, embryos and fetuses, stated that gene therapy does not in principle differ from other forms of highly specialized treatment if it can be established that the genetic material is not unintentionally transferred to germ line cells.

*Id.* Both the French National Advisory Committee on Ethics and the Italian Comitato Nazionale per la Bioetica compare somatic gene therapy to other technically advanced and experimental treatments. *Id.*

92. Commission of the European Communities, *Communication: Biotechnology and the White Paper on Growth, Competitiveness and Employment: Preparing the Next Stage* at 4-5 (1994) [hereinafter *Commission Communication*], in COMMISSION OF THE EUROPEAN COMMUNITIES, *ETHICS AND BIOTECHNOLOGY: INFORMATION DOSSIER ON THE GROUP OF ADVISERS ON ETHICAL IMPLICATIONS OF BIOTECHNOLOGY 26-27* (May 1994) [hereinafter *COMMISSION DOSSIER*].

93. Commission of the European Communities, *Activities of the European Commission in the Field of Bioethics* at 6-7 (1994) [hereinafter *Commission Activities*], in *COMMISSION DOSSIER*, *supra* note 92, at 50-51.

94. *ARCHER REPORT*, *supra* note 6, at 7-8.

95. *Ethics*, *supra* note 15, at 226. By comparison, all protocols in the United States are subject to the regulations of the National Institutes of Health's Recombinant DNA Advisory Committee ("RAC") and the Food and Drug Administration ("FDA"), which have been responsible for developing a regulatory framework and technical standards for academic and commercial gene therapy researchers. *Id.* The guidelines of RAC and the FDA have provided researchers, scientific institutions, and pharmaceutical companies in the United States with uniform, comprehensive parameters within which to operate. *Id.* The United States continues to lead in the field, devoting extensive resources to gene therapy. *Id.* Thus, gene therapy research and product development are progressing rapidly. *Id.*

## 1. Germline Gene Therapy

Germline gene therapy research in Europe, as elsewhere, is currently limited to trials that do not involve human subjects, such as the creation of transgenic animals.<sup>96</sup> Although germline gene therapy may prove to be the only means of treating certain diseases,<sup>97</sup> most experts agree that the application of germline gene therapy in humans is too dangerous given the present state of knowledge.<sup>98</sup> In fact, the European Parliament issued a resolution in 1989<sup>99</sup> formally prohibiting experiments aimed at modifying the human genetic blueprint,<sup>100</sup> providing for criminal prosecution of gene transferral into human gametes,<sup>101</sup> and stating that each modification of the human genome represents an unacceptable and unjustifiable distortion of the human identity.<sup>102</sup>

## 2. Somatic Gene Therapy

Consensus on the desirability of somatic gene therapy is greater than for germline gene therapy.<sup>103</sup> Because prospects for agreement on many aspects of somatic gene therapy are not evident among the Member States,<sup>104</sup> no attempts to articulate comprehensive, Union-wide regulations have been made.<sup>105</sup> The Member States, therefore, have undertaken gene therapy regulation independently.<sup>106</sup>

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96. BIOETHICS IN EUROPE, *supra* note 33, at 89.

97. ARCHER REPORT, *supra* note 6, at 11. At its 1990 Conference, the Council for International Organizations of Medical Sciences declared that continued discussion of germline gene therapy was essential, as the modification of human germ cells for therapeutic or preventive purposes not presently in prospect might be the only means of treating certain conditions. *Id.*

98. See *supra* notes 49-53 and accompanying text (discussing serious implications of germline gene therapy experiments given power to alter genetic blueprint of future generations).

99. Parliament Resolution on Ethical and Legal Problems of Genetic Manipulations A2-327/88 (1988).

100. *Id.*

101. *Id.*

102. *Id.*

103. *Id.* The Resolution stated that somatic gene therapy should be supported and a list of diseases treatable through gene therapy created. *Id.*

104. *Human GT*, *supra* note 8, at 812.

105. BIOETHICS IN EUROPE, *supra* note 33, at 87.

106. *Id.* at 86-88.

## a. Disparate National Efforts

The task of establishing guidelines for somatic gene therapy has been left to numerous local and national bodies,<sup>107</sup> including ethics committees,<sup>108</sup> scientific institutions, public interest groups,<sup>109</sup> and governmental agencies.<sup>110</sup> Having studied the implications and applications of somatic gene therapy, these bodies have articulated various sets of conditions to be met and precautions to be taken when conducting research in the field.<sup>111</sup> Although some common general elements may be found in most of these sets of recommendations,<sup>112</sup> they usually differ in other ways.<sup>113</sup>

In Italy, where the first European clinical trial of somatic gene therapy in humans was performed,<sup>114</sup> the Minister of Health established the Commission of Inquiry on Genetic Engineering in 1985.<sup>115</sup> This commission's final report offered a positive opinion of somatic gene therapy.<sup>116</sup> In February 1991, the Comitato Nazionale per la Bioetica<sup>117</sup> ("Comitato") published a report favorable to somatic gene therapy.<sup>118</sup> In this report, the Comitato equated somatic gene therapy with other experimen-

107. *Id.* at 86-87.

108. *Id.* Examples of such committees are the Comitato Nazionale per la Bioetica [National Committee for Bioethics] in Italy and the Comité Consultatif National d'Ethique [National Advisory Committee on Ethics] in France. *Id.* at 87. In the United Kingdom, the Department of Health established the Special Committee on the Ethics of Gene Therapy in 1989. *Id.* Chaired by Sir Cecil Clothier, the Committee issued a report ("Clothier Report") in favor of somatic gene therapy in January of 1992. *Id.*

109. *Id.* For example, the Genetic Interest Group ("GIG"), a public interest group in the United Kingdom, has published a position paper supporting the use of somatic gene therapy for the treatment of human genetic disorders. *Id.*

110. Thomas Tursz, *Protocole de transfert d'un gène marqueur par un adénovirus recombinant déficient administré par voie intra-tumorale directe sous contrôle fibroscopique dans les cancers broncho-pulmonaires humains* [Protocol for the Transfer of a Reporter Gene by Recombination Defective Adenovirus Administered by Direct Intratumoral Means Under Fibroscopic Control in Human Broncho-Pulmonary Cancers] (1993) [hereinafter *Tursz Protocol*]. In France, for example, the Ministry of Higher Education and Research and the Ministry of Health both oversee gene therapy research. *Id.* at 53.

111. *BIOETHICS IN EUROPE*, *supra* note 33, at 86-87.

112. *See supra* note 57 and accompanying text (discussing widely-recognized general guidelines for clinical research).

113. *ARCHER REPORT*, *supra* note 6, at 7-8.

114. *Human GT*, *supra* note 8, at 811.

115. *BIOETHICS IN EUROPE*, *supra* note 33, at 87.

116. *Id.*

117. *Id.* [National Committee for Bioethics].

118. *Id.*

tal, high-technology therapies, finding trials in human subjects permissible.<sup>119</sup> The Comitato also recommended that a national authority overlook somatic gene therapy.<sup>120</sup> This national authority would be responsible for updating the list of diseases for which somatic gene therapy treatment is allowed, developing guidelines for somatic gene therapy research, and monitoring the results of ongoing trials.<sup>121</sup>

In Germany, the Bundestag Commission of Inquiry on Genetic Engineering ("BCI") concluded in its final report, in 1987, that somatic gene therapy was justifiable and similar to the transfer of living material.<sup>122</sup> The BCI, however, encouraged the practice of providing somatic gene therapy patients with additional medical advice from an independent physician.<sup>123</sup> The BCI also requested that a clear definition of the medical indications of somatic gene therapy be articulated in co-operation with the Ethics Commission of the Federal Chamber of Physicians.<sup>124</sup> In 1989, the Federal Chamber of Physicians published guidelines for somatic gene therapy protocols.<sup>125</sup> In addition, local institutional review boards and ethics committees must approve somatic gene therapy trials.<sup>126</sup>

In France, the Comité Consultatif National d'Ethique<sup>127</sup> ("CCNE") published an opinion on somatic gene therapy in December 1990.<sup>128</sup> The CCNE raised no objections to somatic gene therapy in the opinion.<sup>129</sup> The CCNE recommended, however, that somatic gene therapy be restricted to serious hereditary diseases.<sup>130</sup> In 1993, the CCNE recommended that somatic gene therapy be governed by Law No. 88-1138<sup>131</sup> ("Loi Huriet")

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119. *Id.*

120. *Id.* at 88.

121. *Id.*

122. *Id.* at 87.

123. *Id.* at 88.

124. *Id.*

125. *Id.* The Federal Chamber of Physicians found that several diseases did not meet the requisite genetic criteria, excluding these diseases from its list of diseases for which somatic gene therapy treatment is permissible. *Id.*

126. ARCHER REPORT, *supra* note 6, at 8.

127. BIOETHICS IN EUROPE, *supra* note 33, at 88 [National Advisory Committee on Ethics].

128. *Id.*

129. *Id.* at 87.

130. *Id.* at 88.

131. Loi No. 88-1138 du 20 décembre 1988, J.O., Dec. 22, 1988, at 16,032 (relative

on biomedical experimentation on human beings.<sup>132</sup> Thus, somatic gene therapy protocols must be evaluated by the local research ethics committees in addition to other national bodies.<sup>133</sup>

#### b. Applicable EU Directives

Because somatic gene therapy is not considerably different from other technologically advanced therapies,<sup>134</sup> certain of its elements, such as the viral vectors<sup>135</sup> used in some instances,<sup>136</sup> are governed by preexisting broader biotechnology regulations,<sup>137</sup> such as Council Directives 90/219 on the contained use of genetically modified organisms<sup>138</sup> and 90/220 on the deliberate release into the environment of genetically modified organisms.<sup>139</sup> Since the Directives' entry into force on October 23, 1991,<sup>140</sup> Member States have adopted or are in the process of adopting the necessary implementing legislation.<sup>141</sup> Countries with more vigorous biotechnology sectors are reporting releases in accordance with Council Directive 90/220.<sup>142</sup>

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à la protection des personnes qui se prêtent à des recherches biomédicales [relating to the protection of persons lending themselves to biomedical research]).

132. ARCHER REPORT, *supra* note 6, at 7.

133. *Id.*; see *Tursz Protocol*, *supra* note 110. In this protocol for a somatic gene therapy trial for human broncho-pulmonary cancer performed in France in the summer of 1994, Professor Tursz included copies of the correspondence with and authorizations from the various advisory committees for the protection of individuals. *Id.* at 53-64. As for all trials in France, Professor Tursz's protocol had to receive the approval of the CCNE, la Commission du Génie Génétique du Ministère de l'Enseignement Supérieur et de la Recherche [Commission on Genetic Engineering of the Ministry of Higher Education and Research], la Commission du Génie Biomoléculaire du Ministère de l'Agriculture et de la Pêche [Commission on Biomolecular Engineering of the Ministry of Agriculture and Fishing], and le Groupe d'Experts sur la Sûreté Virale des Médicaments du Ministère de la Santé [Group of Experts on the Viral Safety of Medicines of the Ministry of Health]. *Id.* at 54-62. In addition, the approval of the specific local committee was also required, in this case le Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Bicêtre [Advisory Committee on the Protection of People in Biomedical Research of the municipality of Bicêtre]. *Id.* at 63-64.

134. BIOETHICS IN EUROPE, *supra* note 33, at 85.

135. See *supra* note 38 (disussing gene insertion techniques).

136. *Id.*

137. *Commission Communication*, *supra* note 92, at 4-5, in COMMISSION DOSSIER, *supra* note 92, at 26-27.

138. Council Directive No. 90/219, O.J. L 117/1 (1990).

139. Council Directive No. 90/220, O.J. L 117/15 (1990).

140. *Commission Communication*, *supra* note 92, at 15-17, in COMMISSION DOSSIER, *supra* note 92, at 37-39.

141. *Id.*

142. *Id.*

### c. The European Medicines Evaluation Agency

Besides such general biotechnology guidelines, certain other aspects of somatic gene therapy will come under the control of the European Medicines Evaluation Agency ("EMEA"), which is designed to enforce centralized, Union-wide marketing authorization procedures for medicinal biotechnology products.<sup>143</sup> Created under Council Directive 93/41,<sup>144</sup> the EMEA began operating on January 1, 1995.<sup>145</sup> The EMEA's Management Board is made up of representatives of the Member States, the European Commission, and the European Parliament.<sup>146</sup> Final recommendations by the EMEA's staff are approved and put into law by the Commission of the European Communities ("Commission")<sup>147</sup>.

The ultimate goal of the EMEA is to streamline existing marketing authorization procedures so that patients can benefit from innovative medicinal products simultaneously in all Member States, while at the same time safeguarding maximum standards of public health.<sup>148</sup> To this end, beginning in 1995, the EMEA will impose three registration procedures for medicines in the Union: a centralized EU procedure valid for the fifteen Member States and restricted to certain new medicines;<sup>149</sup> a decentralized procedure, applying to most medicines, based on mutual recognition of national authorizations;<sup>150</sup> and a national procedure for certain medicines restricted to the market of a single Member State.<sup>151</sup>

## II. ANALYSIS OF THE LATEST DEVELOPMENTS

Both the United States and Japan, Europe's primary competitors in biotechnology and genetic research and applications,

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143. *Id.* at 6-7, at 28-29; *Commission Activities, supra* note 93, at 6-7, in COMMISSION DOSSIER, *supra* note 92, at 50-51.

144. Council Directive No. 93/41, O.J. L 214/40 (1993).

145. *Id.*

146. *Commission Activities, supra* note 93, at 7, in COMMISSION DOSSIER, *supra* note 92, at 51.

147. *Id.*

148. *Commission Communication, supra* note 92, at 6, in COMMISSION DOSSIER, *supra* note 92, at 28.

149. *Commission Activities, supra* note 93, at 6, in COMMISSION DOSSIER, *supra* note 92, at 50.

150. *Id.*

151. *Id.*

have established uniform guidelines for gene therapy.<sup>152</sup> The Member States of the European Union, in comparison, have not followed a uniform approach to somatic gene therapy regulation.<sup>153</sup> Determined to remain competitive and to maximize the potential of its infrastructure, the Union decided to reexamine its biotechnology framework.<sup>154</sup> As a result, the European Commission issued *Growth, Competitiveness and Employment: The Challenges and Ways Forward Into the 21st Century, White Paper*<sup>155</sup> ("White Paper"), in 1993, offering an ambitious agenda of harmonization and coordination of research efforts and regulations.<sup>156</sup> The proposals were intended to help the Union realize the full medical and economic promise of gene therapy, ensuring its status as a producer and not simply a consumer of biotechnology products.<sup>157</sup> Former Commission President Jacques Delors also proposed the creation of the Group of Advisers on the Ethical Implications of Biotechnology.<sup>158</sup> In December 1994, one of its members, Professor Luis Archer of Portugal, presented a *Report on Ethical Aspects of Gene Therapy*<sup>159</sup> ("Archer Report"), destined to inform and guide the Commission and the European Parliament ("Parliament") in assessing gene therapy.<sup>160</sup>

#### A. Harmonization in the European Union

Harmonization of Member State laws is necessary for the EU to be successful.<sup>161</sup> Under Article 36 of the EC Treaty, however, Member States are allowed to articulate and retain national regulations.<sup>162</sup> These national regulations often become impedi-

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152. See *supra* note 95 and accompanying text (discussing regulatory framework in United States); David Swinbanks, *Gene Therapy Gets Double Dose of Screening*, 367 NATURE 399 (1994) (discussing regulation of human applications of gene therapy by central government agencies in Japan).

153. ARCHER REPORT, *supra* note 6, at 7-8.

154. White Paper, *supra* note 21.

155. *Id.*

156. *Id.*

157. *Id.*

158. Commission of the European Communities, *European Commission's Group of Advisers on the Ethical Implications of Biotechnology, Activity Report 1991-93* at 6 (1993) [hereinafter *Advisers' Activity Report*], in COMMISSION DOSSIER, *supra* note 92, at 83.

159. ARCHER REPORT, *supra* note 6.

160. *Id.*

161. EC LAW, *supra* note 20, at 428.

162. EC Treaty, *supra* note 18, art. 36.

ments to trade and technological advancements.<sup>163</sup> Thus, Article 100 authorizes the Council of Ministers ("Council") to adopt harmonization measures in the form of directives by a unanimous vote.<sup>164</sup> Article 100a facilitates the adoption of harmonization measures and supplements Article 100, authorizing the Council to adopt harmonization legislation in the form of either directives or regulations by a qualified vote.<sup>165</sup> Article 100a also involves the Parliament in the legislative process.<sup>166</sup>

In the face of increasing barriers due to regulation of rapid technological advances at the Member State level,<sup>167</sup> however, the Commission adopted a "new approach" to technical harmonization in 1985.<sup>168</sup> The "new approach" restricts harmonization of laws to the adoption of essential safety requirements in the form of voluntary technical standards drawn up by relevant industrial standardization bodies.<sup>169</sup> Since the Commission adopted the "new approach," fewer directives have been adopted.<sup>170</sup> Taking the form of "frameworks," those directives that have been adopted set critical minimum health, safety, and technical requirements, with details to be supplied by the Community standards bodies.<sup>171</sup>

### B. *The White Paper*

In 1993, in response to the economic situation of the Member States in a changing environment,<sup>172</sup> and particularly in re-

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163. EC LAW, *supra* note 20, at 428. "Technical barriers also retard technological advance, since they divert capital from basic research to secondary development costs . . . ." *Id.*

164. *Id.* at 428-31.

165. EC Treaty, *supra* note 18, arts. 100-100a; see EC LAW, *supra* note 20, at 439-40. "Directives require implementing Member State laws or regulations within the time period specified (usually two years)." *Id.* at 430. Regulations have immediate force of law throughout the European Union. *Id.*

166. EC LAW, *supra* note 20, at 439-40.

167. *Id.* at 442.

168. *Id.* at 443.

169. *Id.* at 445.

170. *Id.*

171. *Id.* For example, a directive for active implantable medical devices was adopted under the "new approach." *Id.*

172. White Paper, *supra* note 21, COM (93) 700 Final, at 2. The *White Paper* stated that over the last 20 years: the European economy's potential rate of growth has shrunk, from around 4% to around 2.5% a year; unemployment in the Union has been steadily rising from cycle to cycle; the investment ratio has fallen by five percentage points; and the competitive position of the Union in relation to the United States and

sponse to unemployment,<sup>173</sup> the Commission issued the *White Paper*.<sup>174</sup> In the *White Paper*, the Commission proposed solutions to some of these economic problems, identifying promising areas, such as biotechnology, in which the Union could capitalize on its strengths.<sup>175</sup> Thus, the *White Paper* was a call to action for the Union to remain competitive globally, acknowledging that the Member States needed to make a concerted effort to maximize their common potential.<sup>176</sup>

In the *White Paper*, the Commission recognized the need for well-considered regulation in the area of biotechnology, striking the proper balance between the advancement of research and the management of risks.<sup>177</sup> It also offered three major recommendations concerning biotechnology.<sup>178</sup> First, the Union should be willing to review its regulatory framework, given the importance of regulations to research and industry efforts.<sup>179</sup>

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Japan has worsened in the areas of employment, export market shares, research and development and its incorporation into market goods, and the development of new products. *Id.*

173. *Id.*

174. *Id.*

175. *Id.* at 116, ¶ 5.7.

The sectors with the greatest potential for the applications of biotechnology are amongst the most vigorous and competitive sectors in the Community with a long record of sustained growth, productivity increase, and highly competitive trade performance.

The Community firms in these sectors (chemicals, pharmaceuticals, agricultural processing) are leading firms at a global level with important capabilities in the domain of innovation.

Among other factors favouring investment in biotechnology in the Community are the strong science base and infrastructure, the availability of skilled labour, and the high quality of process engineering and production facilities.

*Id.*

176. *Id.* at 5. "We are thus setting out a number of broad guidelines which have a predominantly economic basis, although it will be seen that they cannot be dissociated from the major trends which are affecting society itself: an economy that is healthy, open, decentralized, competitive and based on solidarity." *Id.*

177. *Id.* at 117, ¶ 5.8.

Regulation concerning the safety of applications of the new biotechnology is necessary to ensure harmonization, safety, and public acceptance. However, the current horizontal approach is unfavourably perceived by scientists and industry as introducing constraints on basic and applied research and its diffusion and hence having unfavourable effects on EC competitiveness.

*Id.*

178. *Id.*

179. *Id.* at 118, ¶ 5.9.

Given the importance of regulations for a stable and predictable environment for industry and given that they influence localization factors such as field

Second, the Union must work to reinforce scientific support for regulations.<sup>180</sup> Third, the Union ought to focus on the most vigorous biotechnology research and development domains and to increase coordination of research efforts.<sup>181</sup> Given these recommendations, the Commission made clear that regulation and harmonization<sup>182</sup> are at the core of remaining competitive in biotechnology.<sup>183</sup>

By stressing the outstanding potential of biotechnology for innovation and prosperity, the *White Paper's* recommendations were an impetus in mobilizing people and organizing efforts for the articulation and harmonization of Union policy toward the

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trials and scientific experimentation, the Community should be open to review its regulatory framework with a view to ensuring that advances in scientific knowledge are constantly taken into account and that regulatory oversight is based on potential risks. A greater recourse, where appropriate, to mutual recognition, is warranted to stimulate research activities across Member States. Furthermore, if the Community is to avoid becoming simply a market rather than a producer of biotechnology-derived products then it is vital that Community regulations are harmonized with international practice. The development of standards will supplement regulatory efforts.

*Id.*

180. *Id.*

The Commission intends to make full use of the possibilities which exist in the present regulatory framework on flexibility and simplification of procedures as well as for technical adaptation. To sustain a high level of environmental protection and to underpin public acceptance, it is important to reinforce and pool the scientific support for regulations. An advisory scientific body at Community level for biotechnology diffusion drawing on the scientific expertise within and at the disposal of the existing committees at national and Community level . . . could play a crucial role in intensifying scientific collaboration and in providing the needed support for a harmonized approach of the development of risk assessments underlying product approval. This body could also advise on the development of a further Community strategy for biotechnology.

*Id.*

181. *Id.*

Since the Community is not matching efforts elsewhere in research and development expenditure, it needs to compensate for this through focusing on the most vigorous biotechnology research and development domains and increased coordination between the Community and Member States in order to avoid duplication, encourage collaborative research and improve efficiency of expenditure on research and development.

*Id.*

182. *Supra* notes 161-71 and accompanying text (discussing benefits of harmonization).

183. *See supra* note 179 and accompanying text (discussing efforts Union must make to remain competitive).

field.<sup>184</sup> In a subsequent communication, however, the Commission, after highlighting some of the recommendations of the *White Paper*, proposed postponing any major decisions until 1997.<sup>185</sup> The Commission stated that a review of the regulatory framework would be warranted in light of new developments.<sup>186</sup>

### C. *The Group of Advisers*

Recognizing that neither the Commission nor the Parliament possessed the requisite knowledge to make informed decisions affecting high technology fields,<sup>187</sup> and on the basis of a proposal by then Commission President Jacques Delors, the Commission created the Group of Advisers on the Ethical Implications of Biotechnology ("Group of Advisers") on November 20, 1991.<sup>188</sup> The Group of Advisers is designed to report to the Commission on scientific matters that either the Commission or the Group on its own initiative decides to investigate.<sup>189</sup> The

184. *Commission Communication*, *supra* note 92, at 1, in *COMMISSION DOSSIER*, *supra* note 92, at 23.

185. *Id.* at 7, in *COMMISSION DOSSIER*, *supra* note 92, at 29.

186. *Id.*

187. President Jacques Delors & Noëlle Lenoir, Press Conference, Brussels, 24 May 1994 [hereinafter Press Conference], in *COMMISSION DOSSIER*, *supra* note 92, at 12.

Ni la Commission, ni le Parlement européen, ni le Conseil ne peuvent trouver dans leurs connaissances les éléments suffisants pour trancher certains problèmes fondamentaux; et pourtant, ils sont obligés à prendre des décisions. C'est pourquoi ils demandent l'avis de personnes particulièrement compétentes et totalement indépendantes, qui ne reçoivent aucune instruction . . . . [I]l est absolument indispensable que les décideurs disposent d'éléments qui leur permettent de décider et d'informer objectivement l'opinion publique, en dehors des pressions des lobbies et d'une certaine presse.

*Id.* [Neither the Commission, the European Parliament, nor the Council can find in their knowledge the necessary elements to decide certain fundamental problems; and yet, they are forced to make these decisions. Such is the reason why they seek the advice of particularly competent and totally independent persons who receive no instructions . . . . [I]t is absolutely indispensable for the decision-makers to have access to elements which permit them to decide and to inform the public opinion objectively, outside the pressures of lobbies and a certain press.] (translation by Note Author).

188. *Commission Activities*, *supra* note 93, at 1, in *COMMISSION DOSSIER*, *supra* note 92, at 45. "The Group of Advisers was set up in November 1991 following the Commission's communication entitled 'Promoting the Competitive Environment for Industrial Activities Based on Biotechnology Within the Community.'" *Id.*; see *Advisers' Activity Report*, *supra* note 158, at 6, in *COMMISSION DOSSIER*, *supra* note 92, at 83 (discussing Group of Advisers' creation and role).

189. Press Conference, *supra* note 187, at 1, in *COMMISSION DOSSIER*, *supra* note 92, at 12. "Mme Lenoir a insisté sur le caractère libre et indépendant des travaux du groupe, qui peut entreprendre l'étude d'un problème aussi bien de son initiative qu'à la demande de la Commission." *Id.* ["Mrs. Lenoir insisted on the free and in-

Group is intended to remain partly autonomous, distinguishing it as an objective source of information for policy makers.<sup>190</sup> Now in its second term,<sup>191</sup> the Group has nine members.<sup>192</sup> One of them, Professor Luis Archer, a geneticist from Portugal, was asked to report on gene therapy.<sup>193</sup> Professor Archer's findings are intended to guide the Commission as it considers pertinent regulations in the future.<sup>194</sup>

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dependant character of the work of the group, which can undertake the study of a problem of its own initiative just as well as at the Commission's request." ] (translation by Note Author).

190. *Id.*

191. *Commission Activities*, *supra* note 93, at 1, in *COMMISSION DOSSIER*, *supra* note 92, at 45.

The Group of Advisers issued three opinions during its first term (1991-93). The first was on BST (bovine somatotropin), the second was on the legal protection of biotechnological inventions and the third on products derived from human blood or human plasma. The group is currently looking at the ethical implications of gene therapy, the use of transgenic animals and prenatal diagnosis.

*Id.*

192. *Advisers' Activity Report*, *supra* note 158, at 6, in *COMMISSION DOSSIER*, *supra* note 92, at 83. "In view of the nature of the interests at stake a pluralist and multidisciplinary approach was called for. The members of the Group of Advisers are accordingly drawn from the worlds of science, law, philosophy and politics. Each member serves a two-year term." *Id.*; see Commission of the European Communities, *Composition of the Group of Advisers on Ethical Implications of Biotechnology* (1993) [hereinafter *Composition*], in *COMMISSION DOSSIER*, *supra* note 92, at 73-76. The members of the Group of Advisers are: Mrs. Noëlle Lenoir, a French politician and President of the Group of Advisers; Prof. Luis Archer, a Portuguese scientist; Prof. Gilbert Hottois, a Belgian philosophy professor; Dr. Anne McLaren, a British scientist; Prof. Dietmar Mieth, a German theology professor; Dr. Margareta Mikkelsen, a Danish physician; Dr. Octavi Quintana Trias, a Spanish physician; Prof. Stefano Rodota, an Italian law professor; and Prof. Egbert Schrotten, a Dutch theology professor. *Id.*

193. *Advisers' Activity Report*, *supra* note 158, at 7, in *COMMISSION DOSSIER*, *supra* note 92, at 84.

One member is appointed rapporteur for each topic selected, depending on his or her expertise and interests. Once the research is completed, the rapporteur drafts a report accompanied by a draft opinion, which is then considered by the Group. Dissenting opinions may also be attached.

*Id.*; see *id.* at 11-12, at 88-89 (discussing Group of Advisers' works in progress).

194. *Press Conference*, *supra* note 187, at 1, in *COMMISSION DOSSIER*, *supra* note 92, at 12. "Le groupe va franchir a présent une nouvelle étape. Grâce aux moyens accrus dont il disposera, il pourra notamment: . . . aborder aussi des 'sujets d'anticipation' comme la médecine génétique . . ." *Id.* ["The group will presently reach a new stage. Due to the increased means at its disposal, it will be able to: . . . investigate also upcoming subjects such gene therapy . . ."] (translation by Note Author); see *Advisers' Activity Report*, *supra* note 158, at 7, in *COMMISSION DOSSIER*, *supra* note 92, at 84. "The Group's opinions are purely advisory. They are designed to guide the Commission in biotechnology-related activities to enable it to lay down ethically responsible rules." *Id.*

### D. *The Archer Report*

On September 23, 1993, the Commission requested an evaluation of gene therapy from the Group of Advisers.<sup>195</sup> In response to the Commission's request, Professor Archer presented a *Report on Ethical Aspects of Gene Therapy* ("*Archer Report*") on December 13, 1994.<sup>196</sup> The *Archer Report* consists of four parts: 1) Definitions;<sup>197</sup> 2) Ethical Evaluation of Somatic Gene Therapy;<sup>198</sup> 3) Ethical Review of Somatic Gene Therapy Protocols and Products;<sup>199</sup> and 4) Ethical Evaluation of Germline Gene Therapy.<sup>200</sup>

#### 1. Definitions

The first part of the *Archer Report* reviewed briefly some of the background scientific information.<sup>201</sup> It defined gene therapy and distinguished between somatic and germline gene therapy, outlining the implications of each.<sup>202</sup> The *Archer Report* also stated that it would not cover enhancement genetic engineering.<sup>203</sup>

#### 2. Ethical Evaluation of Somatic Gene Therapy

The second part of the *Archer Report* began by stressing that gene therapy remained in its experimental stages.<sup>204</sup> As such, somatic gene therapy trials should currently be subjected to the widely-recognized ethical principles for experimental therapies

195. *Advisers' Activity Report*, *supra* note 158, at 12, in *COMMISSION DOSSIER*, *supra* note 92, at 89.

196. *ARCHER REPORT*, *supra* note 6.

197. *Id.* at 1.

198. *Id.* at 3.

199. *Id.* at 7.

200. *Id.* at 10.

201. *Id.* at 1.

202. *Id.*

203. *Id.* at 2.

At present, somatic gene therapy techniques are considered ethically admissible only for the treatment or prevention of serious diseases . . . the latter being defined as diseases which cause significant suffering and premature death. . . . Consequently, enhancement genetic engineering is presently excluded from the ethically admissible clinical trials and, for that reason, will not be considered in this Report.

*Id.*

204. *Id.* at 3.

of the Helsinki Declaration<sup>205</sup> and the Belmont Report.<sup>206</sup> The *Archer Report* summarized these principles in four broad points along which it structured its discussion: benefits for the patient should be expected;<sup>207</sup> disproportionate risks should be excluded;<sup>208</sup> the dignity and autonomy of the person should be respected;<sup>209</sup> and justice should be attained.<sup>210</sup>

#### a. Benefits

In considering the benefits to be derived from somatic gene therapy, the *Archer Report* highlighted the promise somatic gene therapy holds in alleviating, curing, or preventing both genetic and acquired diseases.<sup>211</sup> The *Archer Report* emphasized the promise somatic gene therapy holds in the fight against diseases for which there are only poor or no alternative therapies.<sup>212</sup> Professor Archer also stressed the profound impact it will have on medicine, especially as the use of in vivo techniques facilitating and broadening the administration of gene therapy increases.<sup>213</sup>

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205. HELSINKI DECLARATION, *supra* note 57; *see supra* note 57 and accompanying text (discussing widely-recognized general guidelines of Helsinki Declaration).

206. BELMONT REPORT, *supra* note 57.

207. ARCHER REPORT, *supra* note 6, at 3.

208. *Id.*

209. *Id.*

210. *Id.*

211. *Id.*

212. *Id.* at 3-4.

In addition to the adenosine deaminase (ADA) deficiency, other genetic diseases have been the object of gene therapy protocols, namely familial hypercholesterolemia, cystic fibrosis, Gaucher disease, glucocerebrosidase and hemophilia B. Acquired diseases like AIDS, cardiovascular diseases, and cancer are also being contemplated by gene therapy. As a matter of fact, cancer is the disease for which about two thirds of gene therapy protocols have been designed.

*Id.*

213. *Id.* at 3.

Initially, somatic gene therapy was always performed *ex vivo*. This means that target cells were removed from the patient, grown in culture *in vitro*, genetically modified by the use of an appropriate vector, and then harvested and finally reimplanted in the same patient. More recently, an *in vivo* strategy started being developed which involves direct administration of the gene-carrying vector into the patient's organism. As this latter strategy tends to be used more progressively, each of the individual clinical trials will be less dependent on sophisticated high-technology, and the ethical use of somatic gene therapy will become much easier and more widespread. It will then have a profound impact on medicine.

*Id.*

## b. Risks

In assessing the risks of somatic gene therapy, the *Archer Report* raised two considerations.<sup>214</sup> The first is that risks are present in all aspects of somatic gene therapy, given its experimental nature.<sup>215</sup> Secondly, the risks could not be fully quantified until greater knowledge was accumulated, especially as to secondary side effects.<sup>216</sup>

The *Archer Report* highlighted the need to strike a balance between permissiveness and control in regulating somatic gene therapy.<sup>217</sup> This balance is important to ensure that the benefits of somatic gene therapy may continue to be available without serious incidents threatening the entire endeavor.<sup>218</sup> The *Archer Report* stated that most existing regulations recognize the need to proceed cautiously in light of the risks.<sup>219</sup> Most of these regulations, therefore, prescribe that the diseases initially selected for gene therapy should be serious, and lack effective alternative treatments.<sup>220</sup> Only after such trials have proven safe and effective should researchers and physicians contemplate treatment of

214. *Id.* at 4-5.

215. *Id.* at 4.

216. *Id.*

In order to evaluate risks, sufficient scientific knowledge on the pathophysiology of the disease and on the molecular biology of the gene concerned, as well as its vector, are required. This knowledge, together with animal experimentation (including that [on] non-human primates), should show whether or not (i) the therapeutic gene is expected to be inserted at the right place in the target cells and to remain there long enough to be effective, (ii) the introduced gene is appropriately regulated, producing acceptable amounts of the product and (iii) there are no secondary effects. This latter requirement is, presently, very difficult to assess.

*Id.*

217. *Id.*

218. *Id.*

It is important that the public is aware of these potential risks, so that the review and oversight of gene therapy protocols do not become too relaxed and when the first serious problems come, the public does not force a halt or significant slowdown of gene therapy research, which should, nevertheless, continue and be encouraged to the benefit of so many patients.

*Id.*

219. *Id.* at 4.

220. *Id.*; see *id.* n.2 (referring specifically to documents from France and United Kingdom); *Gene Therapy in Man: Recommendations of European Medical Research Councils*, 1 *LANCET*, 1271, 1271 (1988) [hereinafter *Recommendations of Councils*]. The guidelines of the European Medical Research Council mention "diseases which are invariably fatal or severely disabling and for which current therapies . . . are not always feasible or carry a high level of risk." *Id.*

less burdensome diseases for which alternative treatments exist.<sup>221</sup>

### c. Dignity and Autonomy

The *Archer Report* reiterated the conventional need to respect the dignity, health, and privacy of patients undergoing somatic gene therapy.<sup>222</sup> It also emphasized the importance of informed consent and full disclosure to the patient.<sup>223</sup> Once again, however, the experimental nature of somatic gene therapy was such that the *Archer Report* was compelled to articulate a standard of disclosure to patients higher than that for conventional treatments.<sup>224</sup>

### d. Justice

The *Archer Report* addressed the need to select patients and the diseases to be treated by somatic gene therapy fairly.<sup>225</sup> Somatic gene therapy also was not to be driven entirely by the economic concerns of the biomedical industry, overlooking rarer diseases while pushing research to combat more common and hence more lucrative ones.<sup>226</sup> This is a problematical consideration in the traditional European context of socialized medicine<sup>227</sup> and given the goals of the *White Paper*.<sup>228</sup>

## 3. Ethical Review of Somatic Gene Therapy Protocols and Products

The third part of the *Archer Report* confirmed that most Eu-

221. ARCHER REPORT, *supra* note 6, at 5; see *Recommendations of Councils*, *supra* note 220, at 1271 (discussing guidelines of the European Medical Research Councils).

222. ARCHER REPORT, *supra* note 6, at 5.

223. *Id.*

224. *Id.* "[T]he interests of the patient's health should always prevail over the research interests." *Id.*

In addition, informed consent of the patient should be obtained, noting that, due to the declared uncertainty implicit in experimental treatments, the standard of disclosure for patient involvement and authorization should be higher than the standard required for conventional treatments.

*Id.*

225. *Id.* at 5.

226. *Id.* "Special care should be taken of 'orphan diseases' (those affecting few patients) which are . . . given great social support but are of little or no interest to the medicinal industry." *Id.*

227. *Id.* at 6.

228. White Paper, *supra* note 21.

European regulatory efforts to date have occurred at the various national levels.<sup>229</sup> It supported this point by highlighting the fact that, in considering gene therapy regulation and making their recommendations, various European advisory bodies did not look beyond the national level.<sup>230</sup> After briefly reviewing the protocols and regulations of the United Kingdom, France, the Netherlands, Italy, and Germany,<sup>231</sup> the *Archer Report* concluded that well-considered, Union-wide legislation was desirable, although some broad EU biotechnology regulations apply to certain aspects of gene therapy.<sup>232</sup> The *Archer Report* maintained that the articulation and implementation of such a framework would result in a fuller realization of the potential of gene therapy in Europe.<sup>233</sup> Reflecting some of the broad goals of the

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229. ARCHER REPORT, *supra* note 6, at 7.

Any somatic gene therapy protocol must be assessed as to the ethical aspects. The natural places for such assessment are the local research ethics committees. They are supposed to be advisory bodies, leaving the responsibility of any accident with the medical team. However, there is a tendency in several European countries, as well as in the United States, to look for a reenforcement of the action of the local committees by one or more national supervisory bodies.

*Id.*

230. *Id.* at 8.

The 1988 Guidelines from the European Medical Research Councils recommend that 'a national body should consider all proposals for human gene therapy and ensure the application of agreed national guidelines. Early trials should be monitored by a central body.' Since 1989, the Council of Europe has recommended 'national or regional multidisciplinary bodies' with tasks of informing, guiding, monitoring and evaluating results. At the First Round Table of Ethics Committees (Madrid, 1992), the Council of Europe suggested that national ethics committees be consulted as an instance complementary to the local ethics committees, in regard to formulation of standards, support, oversight, and evaluation.

*Id.* (citations omitted).

231. *Id.* at 7-8; *see supra* notes 107-33 and accompanying text (discussing disparate national regulatory efforts in Member States).

232. ARCHER REPORT, *supra* note 6, at 8.

Directives 90/219/EEC and 90/220/EEC from the European Union apply to certain phases of gene therapy protocols, but do not cover, for instance, the clinical trials. These are regulated, in some European countries, by specific legislation. It might be desirable to have, on this, a legal document at European level.

*Id.*; *see supra* notes 138-39 and accompanying text (discussing Directives 90/219 and 90/220).

233. ARCHER REPORT, *supra* note 6, at 8.

An important ethical requirement for the whole net of control mechanisms is that, in addition to the quality of the ethical argument, they are efficient and do not cause unnecessary delays. Illnesses will not wait for a more convenient

*White Paper*, it envisioned involving all citizens of the EU in this process.<sup>234</sup>

This part of the *Archer Report* also considered how the emerging market for gene therapy products would be regulated.<sup>235</sup> Given the great market potential of gene therapy products, it emphasized the need for appropriate regulation of manufacturing and marketing efforts.<sup>236</sup> Certain aspects of research and commercially manufactured gene therapy products will be regulated in three ways:<sup>237</sup> by general Community legislation for biotechnological products;<sup>238</sup> by the Code for Good Clinical Practice for Trials on Medicinal Products in the European Community;<sup>239</sup> and by the marketing authorizations of the EMEA.<sup>240</sup> The *Archer Report* also mentioned that additional guidelines would be issued in the course of 1995.<sup>241</sup>

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time and the patients need any help that can be given to them now. For such efficiency, the harmonization and partial standardization of all European evaluation processes might be helpful.

*Id.*

234. *Id.*

Another important ethical requirement is the transparency of the evaluation processes. They should be regularly published, giving to the public an objective information on the scientific and ethical aspects of gene therapy developments, and promoting the close participation of European citizens in the democratic construction of our science, technology, and ethics.

*Id.*

235. *Id.*

236. *Id.*

It is expected that, within a 3-5 years period, products for gene therapy are ready to come on the market. The gene therapy market is expected to be, in the near future, very large and the economic impact on biomedical equipment and gene therapy consumables will be considerable. It is important, therefore, that the manufacturing, commercialization, and distribution of gene therapy products are appropriately regulated.

*Id.*

237. *Id.* at 9.

238. *See supra* notes 138-39 and accompanying text (discussing Council Directive 90/219/EEC on the contained use of genetically modified microorganisms and Council Directive 90/220/EEC on the deliberate release of genetically modified organisms into the environment).

239. ARCHER REPORT, *supra* note 6, at 9. "This code includes the requirements for informed consent of the subject taking part in the trial and for the review of the local, pluridisciplinary and independent ethics committees." *Id.*

240. *See supra* notes 143-51 and accompanying text (discussing function and scope of EMEA regulation).

241. ARCHER REPORT, *supra* note 6, at 9. "Additional guidelines for specific quality and safety requirements in the manufacture and control of products for gene therapy will be available in 1995." *Id.*

#### 4. Ethical Evaluation of Germline Gene Therapy

Finally, the fourth part of the *Archer Report* addressed germline gene therapy.<sup>242</sup> It began by stating that the present state of knowledge for germline gene therapy is entirely insufficient.<sup>243</sup> Then, the *Archer Report* assessed the status of germline gene therapy along the same four principles it used in its evaluation of somatic gene therapy: benefits, risks, dignity and autonomy of the person, and justice.<sup>244</sup>

##### a. Benefits

In assessing the benefits of germline gene therapy, the *Archer Report* first recognized that in a large number of cases there are easier and safer alternatives.<sup>245</sup> In the remainder of cases, however, germline gene therapy is the better, if not the only, alternative.<sup>246</sup> As the only technique capable of engendering a genetic change in all the cells of an individual, germline

242. *Id.* at 10.

243. *Id.*

The present state of knowledge in germ-line gene therapy can be described as follows: a) there is no sufficient experience and monitoring of somatic gene therapy as to clearly establish the safety and effectiveness of its use and, much less, of its extension to the self-perpetuating germ-line; b) [there] are no sufficient animal studies on germ-line gene therapy applicable to humans; c) there is not yet any clinically useful and clearly proposed protocol for germ-line gene therapy, defining, namely, the vectors to be used and the potential target cells . . . .

*Id.*

244. *Id.*

245. *Id.* “[F]or the vast majority of the cases, only one of the parents is carrying the genetic defect. In such cases, it would be easier and safer to select healthy embryos, by preimplantation diagnosis, than to perform gene therapy on those which carry the defect.” *Id.*

246. *Id.* at 10 & n.5 (quoting Pierre M. Lehn, *Scientific Aspects of Gene Therapy* 35 (forthcoming 1995)).

Only in the highly exceptional and unlikely cases of embryos produced by two individuals both being recessive homozygous for the same defect would gene therapy be useful, since all embryos would then be affected. It can be answered, however, that other and more frequent cases in genetics could be mentioned where preimplantation diagnosis is of no help. . . . This is the case of ‘parents who do not wish to have heterozygous children in order to spare them the difficult decisions they would have when they in turn came to have children’. . . . The same applies to diseases due to mitochondrial gene defects. . . . Gene therapy of spermatogonia might be the only possible option for those who have serious ethical objections against preimplantation diagnosis and destruction of pre-embryos.

*Id.*

gene therapy is unique and its potential great.<sup>247</sup> Gene therapy holds such promise because it can eradicate problems at their core instead of merely treating their manifestations.<sup>248</sup> The *Archer Report*, therefore, described germline gene therapy as a "medical imperative."<sup>249</sup>

#### b. Risks

In considering the risks of germline gene therapy, the *Archer Report* referred to its evaluation of the present state of knowledge.<sup>250</sup> Hence, it concluded that presently, and for a number of years to come, the risks could not be evaluated accurately.<sup>251</sup> The *Archer Report* also noted that the objections of some to germline gene therapy were based on the technique per se, aside from a consideration of the risks involved.<sup>252</sup>

#### c. Dignity and Autonomy

This portion of the *Archer Report* was based on the assump-

247. *Id.* at 11 (quoting COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES XXIVTH ROUND TABLE MEETING REPORT (1990)).

[G]erm-line [gene] therapy might be 'the only means of treating certain conditions, so continued discussion of both its technical and its ethical aspects is therefore essential . . . . The option of germ cell gene therapy must not be prematurely foreclosed. It may some day offer clinical benefits attainable in no other way. Science has confounded many predictions about what is technically possible and what is not. Germ cell therapy might eventually permit more effective prevention of genetic disease, rather than treatment of its effects.

*Id.*

248. *Id.* "Another benefit is its prophylactic efficiency. By preventing transmission at the affected genes, germ-line gene therapy would dispense with the need to perform costly and risky somatic gene therapy in multiple subjects of successive generations." *Id.*

249. *Id.* at 11.

The moral mandate of medicine is to cure, to care, and to prevent diseases, alleviating suffering as much as possible. Considering that such possibility may be expanded by this self-perpetuating therapy, medicine has a prima facie moral duty to pursue and employ germ-line gene therapy as soon as it is safe.

*Id.*

250. *Id.*

251. *Id.*

It is clear that without risk evaluation, specially considering that any negative effects would be indefinitely perpetuated, to start now any attempt of germ-line therapy in humans would be severely unethical and should be forbidden. This seems to be an unanimous position of all statements produced on the matter by a variety of institutions.

*Id.*

252. *Id.* at 12.

tion that sufficient research revealed germline gene therapy to have negligible side-effects in humans.<sup>253</sup> An ethical evaluation of germline gene therapy under these circumstances raised important issues.<sup>254</sup> The *Archer Report* presented the "slippery slope" argument of some critics of germline gene therapy, envisioning a progression from therapeutic to non-therapeutic uses of germline gene therapy technology.<sup>255</sup> The *Archer Report* also presented the argument of other critics of germline gene therapy who hold that future generations cannot give their informed consent and have the right to inherit an unaltered genome.<sup>256</sup> Though guarded, the *Archer Report's* assessment of germline gene therapy was more positive than that of the critics of germline gene therapy.<sup>257</sup>

#### d. Justice

Finally, the *Archer Report* expressed the opinion that germline gene therapy was not fundamentally objectionable.<sup>258</sup> It stated that the relatively unanimous present opposition to germline gene therapy was due mostly to the current lack of knowledge.<sup>259</sup> Germline gene therapy on human subjects, therefore, was rightfully forbidden.<sup>260</sup>

253. *Id.*

254. *Id.*

255. *Id.* at 13.

256. *Id.*

257. *Id.*

It is not clear why hazards of nature should necessarily be better than achievements of science. . . . This view overlooks the importance of artificial components in our lives and activities. We are artificial beings by our very nature. The human intelligence and the consequent capability of innovation and creativity also belong to nature.

*Id.*

258. *Id.* at 14.

259. *Id.*

The only solid reasons to oppose germ-line gene therapy for the time being are the scientific uncertainties which prevent us from evaluating benefits and risks. As long as this situation persists, any attempt of performing germ-line gene therapy in human subjects would be irresponsible and should be forbidden. As soon as the situation is scientifically clarified, it will have to be ethically reevaluated. . . . [T]he problem will not be insurmountable. In addition, abuses should not be impeditive of fair uses.

*Id.*

260. *Id.*

### III. HARMONIZATION OF GENE THERAPY REGULATION: RECOMMENDATIONS

Because of its potential, the concerns raised by gene therapy cannot be allowed to impede its progress. Because of its risks, however, gene therapy's advances cannot be allowed to proceed unchecked. The tension between these competing considerations highlights the need for sound regulation of gene therapy, establishing clear parameters within which researchers, scientific institutions, and pharmaceutical firms, among others, may operate. In the absence of such a regulatory framework for gene therapy, the field's greatest potential in terms of medical and economic benefits may never be realized. Because comprehensive regulation of gene therapy is not imminent at the level of the European Union,<sup>261</sup> research and clinical efforts will continue to be regulated mostly at the national level of the individual Member States.<sup>262</sup> Given the resources and efforts of the United States,<sup>263</sup> the Union may thereby be putting itself at a serious competitive disadvantage.<sup>264</sup> It may also fail to maximize the medical and economic potential of gene therapy.

#### A. *Effect of the Archer Report*

The *Archer Report* fulfilled its fact-finding purpose of presenting the technology of gene therapy and the accompanying issues.<sup>265</sup> It also recognized the difficulty in reevaluating certain European health care priorities and in overcoming technological disparities among the Member States to make the benefits of gene therapy equally available to all Europeans.<sup>266</sup> Although the

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261. See *supra* notes 185-86 (discussing Commission's wait-and-see approach).

262. ARCHER REPORT, *supra* note 6, at 7-8.

263. See *supra* note 68 and accompanying text (discussing ratio of gene therapy protocols in United States to gene therapy protocols in European Union).

264. Valerie Szczepanik, *Regulation of Biotechnology in the European Community*, 24 LAW & POL'Y INT'L BUS. 617, 619-20 (1993) [hereinafter Szczepanik, *Regulation*].

265. ARCHER REPORT, *supra* note 6.

266. *Id.* at 6.

A second problem of justice refers to the distribution of resources for health care. In contrast to a more utilitarian view in the US, most [E]uropean countries defend that everybody's right to health care is equal. However, the debates on resource allocation have shown that, due to the fast increasing number of new biomedical technologies, scarcity of resources is becoming evident and choices in health care are therefore inevitable. In this same context, socialized medicine, which is traditional in Europe, has recently given some place to forms of medical privatization. These problems of choices in health

*Archer Report* recognized the need for comprehensive Union-wide regulation,<sup>267</sup> it did not offer concrete solutions.<sup>268</sup> The pace of the research, however, is such that if the European Union wishes to attain the goals set in the *White Paper*, capitalizing on the potential of gene therapy to bring prosperity and health equally to the citizens of all the Member States, it must act soon.

### B. *Need for Thoughtful Regulation*

Currently, certain aspects of gene therapy are regulated within the European Union under some broad biotechnology Directives,<sup>269</sup> the recommendations of the EMEA,<sup>270</sup> and any additional guidelines within the individual Member States.<sup>271</sup> Thus, Council Directives 90/219 and 90/220 will control the risks presented by certain elements of gene therapy, such as the viral vectors used to insert functional genes.<sup>272</sup> The regulations of the EMEA will govern the eventual marketing of gene therapy products.<sup>273</sup> In part, it will also ensure that citizens of the Union share equally in the medical benefits of gene therapy.<sup>274</sup> The more fundamental aspects of gene therapy research, however, are not regulated uniformly and are subject to the guidelines of

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care will soon affect gene therapy, specially because this new technology is, at the moment, still very expensive. Criteria for priorities in health care have to be globally studied, discusse[d] and established.

*Id.*; see *id.* n.3, (citing A REPORT FROM THE DUTCH GOVERNMENTAL COMMITTEE ON CHOICES IN HEALTH CARE (1992)). The study provides four criteria to be used in considering whether a given technology is to be considered part of a "basic package" of health care: 1) Is it necessary care, from the community point of view?; 2) Is it demonstrated to be effective?; 3) Is it efficient?; and 4) Can it be left to individual responsibility? *Id.* at 6.

A third problem of justice deals with the distribution of gene therapy centers among the different countries. It would not seem fair that the benefits of this new technology were restricted to industrialized countries. It would be advisable to develop a policy for the promotion of gene therapy applications in developing countries.

*Id.*

267. *Id.* at 8.

268. *Id.*

269. See *supra* notes 138-39 (discussing Council Directives 90/219 and 90/220).

270. See *supra* notes 148-51 and accompanying text (discussing function of EMEA).

271. See *supra* notes 107-33 and accompanying text (discussing regulatory efforts at national levels).

272. See *supra* notes 134-39 and accompanying text (discussing regulation of viral vectors under existing Council Directives).

273. See *supra* notes 148-51 and accompanying text (discussing role of EMEA).

274. *Id.*

the individual Member States.<sup>275</sup>

Thus, researchers throughout the Union are subject to varying restrictions on their work.<sup>276</sup> Because scientific institutions, pharmaceutical firms, and governmental agencies must operate in accordance with pertinent existing regulations in allocating resources for gene therapy research, predictable ground rules and clear regulations could result in more efficient allocations, accelerating the pace of progress.<sup>277</sup> The European Union, therefore, should enact Union-wide gene therapy regulations to create the kind of harmonized and streamlined environment in which academics and industrialists may flourish.

Regulation can also ensure that research is guided by the proper motives. Without clear uniform Union-wide guidelines, the Member State with the most permissive regulatory framework may host the bulk of the research initiatives, possibly to the detriment of the entire endeavor.<sup>278</sup> Ultimately, research must be driven by the most pressing medical needs, not by profit motives.<sup>279</sup> The EU should seize the opportunity it now has to affect the course of the development of gene therapy.

### C. *Need for Harmonization in the European Union*

Given the current levels of infrastructure and investment, no Member State alone is able to compete with the United States in the field of gene therapy.<sup>280</sup> The European Union must,

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275. See *supra* notes 107-33 and accompanying text (discussing regulatory efforts at national levels).

276. *Id.*

277. Szczepanik, *Regulation*, *supra* note 264, at 645. "For industry to make wise investment and development decisions, it must be assured of a stable regulatory environment." *Id.*

Perhaps even more affected than industrialists by the EC's [biotechnology] regulatory scheme are academic researchers, who, unlike their industry counterparts, cannot calculate a profit profile to justify outlay of large amounts of time and money needed to meet regulatory requirements. . . . Another effect will be that only research leading to profit-making will be undertaken, curtailing much-needed basic research with prohibitive costs.

*Id.* at 641-42.

278. See *supra* note 218 (discussing risks of backlash).

279. See *supra* note 226 (defining and discussing orphan diseases).

280. Szczepanik, *Regulation*, *supra* note 264, at 620.

The relative freedom of U.S. industry to pursue a variety of courses in the development of [biotechnology] products also gives the U.S. a comparative advantage. Historically, European countries have hesitated to invest in biotechnology, partially because cultural and legal traditions tended not to pro-

therefore, harmonize the various research efforts within its borders, avoiding the duplication of trials and encouraging cooperation. To achieve this goal, the field cannot be subject to multiple independent sets of standards.

Individual European pharmaceutical companies and scientific institutions in the leading European states will be able to remain in the forefront of innovation and to retain a share of the market for gene therapy products. Biotechnology, and gene therapy in particular, however, have more to offer the Union. In terms of research and medical treatment, gene therapy is labor intensive, potentially employing large numbers of highly skilled professionals.<sup>281</sup> The EU must therefore act to ensure its status as a biotechnology producer, not a mere consumer. Each Member State must share the benefits of this technology, its pursuit elevated and organized above national borders.

Thus, the approach articulated by the Commission in its communication subsequent to the *White Paper* is disconcerting.<sup>282</sup> Vowing to perform the important function of remaining abreast of developments in the field, the Commission instead postpones concrete action. Given Europe's more limited gene therapy research efforts, the Commission should realize the urgency of the need for orchestration.

#### D. *Taking the Proper Steps Forward*

Comprehensive Union-wide regulations for somatic gene therapy should be articulated, agreed upon, and enforced by the Member States as soon as possible. Certain codes of conduct and standards of practice already are widely accepted and could lay the foundation for this effort.<sup>283</sup> Beyond this, concrete efforts should be made to orchestrate research efforts in all Member States.<sup>284</sup> Only then will Europe as a whole be able to re-

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mote venture capital formation and, consequently, risk-taking ventures, placing the EC at a competitive disadvantage from the start. Additionally, government funding has been lower in the EC than in the United States . . . .

281. *White Paper*, *supra* note 21, COM (93) 700 Final, at 115, ¶ 5.6.

282. *Commission Communication*, *supra* note 92, at 7, in COMMISSION DOSSIER, *supra* note 92, at 29. "An ongoing review of the biotechnological regulatory framework shall be carried out as new scientific knowledge and the emerging regulatory practice of major international competitors indicates that this is necessary or desirable." *Id.*

283. See *supra* note 57 and accompanying text (discussing widely-recognized general guidelines for clinical research).

284. *White Paper* *supra* note 21, COM (93) 700 Final, at 117, ¶ 5.9. The *White*

main competitive and derive the full medical and economic benefits of gene therapy.

### CONCLUSION

As outlined in the *White Paper*, Europe is placing great hopes on achieving success in the field of gene therapy. The groundwork to attain the goals of the *White Paper* has not been laid, however. To date, regulation of gene therapy, necessary in structuring the research efforts, has happened haphazardly and independently within the individual Member States. Thus, on an issue of great economic and medical importance to all its citizens, the EU stands fragmented where it should stand as one. If the European Union makes a concerted effort to harmonize its regulatory framework for gene therapy and to orchestrate its research efforts, however, it has every chance of exploiting the full potential of this promising new technology.

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*Paper*, for example, envisages a network of biotechnology science parks throughout the European Union, linking academic institutions and research laboratories. *Id.*