

**NATIONAL REGULATORY FRAMEWORKS
REGARDING HUMAN GENETIC MODIFICATION
TECHNOLOGIES (Somatic and Germline Modification)**

A Report for the Genetics and Public Policy Center

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POLICIES REGARDING HUMAN GENETIC MODIFICATION TECHNOLOGIES

Genetic modification, often referred to as gene therapy, is a procedure whereby the genetic content (DNA sequence) of a cell, many cells or a whole organism is modified. Most often, non-functional or malfunctioning genes are replaced, manipulated or supplemented with healthy genes. In humans, there are two categories of genetic modification: somatic and germline. Somatic gene therapy consists of introducing a gene or gene segment into specific tissues or organs (excluding germline cells or reproductive cells) in a human subject with the aim of treating or curing an existing condition. Unlike germline genetic modification, somatic gene therapy does not alter the genetic make-up of future generations because the altered gene does not exist in reproductive eggs or sperm. Germline gene therapy, on the other hand, is a more controversial technique because the introduction of a gene into germline cells will result in heritable changes that affect future offspring. Germline gene therapy is not currently scientifically possible in humans.

The following report provides a detailed analysis of international policies on genetic modification techniques; particular focus will be on the legal and ethical standards that have been adopted and the regulatory systems that exist to control and govern genetic modification. Among the 16 countries surveyed, it was found that many countries do not have explicit policies regarding gene therapy as it is still considered to be experimental research and not therapeutic treatment. Therefore, policies regarding gene therapy in many countries fall under the scope of existing regulatory systems that govern human clinical trials or biomedical research. It is important to note that there are several international documents that provide guiding principles in the area of human biomedical research. These key documents include: the *World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) 2004* and the *Guidelines for Good Clinical Practice 1996* (adopted by the International Conference on Harmonisation) and the *Statement on Gene Therapy Research 2001* (adopted by the Human Genome Organisation, HUGO). For European countries in particular, the *Convention of Human Rights and Biomedicine 1997* (adopted by the Council of Europe) is applicable to signatory countries.

AUSTRALIA (Federal)

- National Health and Medical Research Council, Medical Research Ethics Committee, *Ethical Aspects of Research in Human Gene Therapy: Report to the NHMRC by the Medical Research Ethics Committee of the NHMRC*, (1987).
- *Therapeutic Goods Act*, (1989),
<http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/frame lodgmen tattachments/C968005F9AFB521ECA2571E2001EAC64>
- National Health and Medical Research Council, *National Statement on Ethical Conduct in Research Involving Humans (Part 12 – Clinical Trials)*, (1999),
<http://www.nhmrc.gov.au/publications/humans/part12.htm>
- National Health Medical Research Council, *Guidelines for Ethical Review of Research Proposals for Human Somatic Cell Gene Therapy and Related Therapies*, (1999), http://www.nhmrc.gov.au/publications/_files/e38.pdf
- National Health Medical Research Council, *Guidelines for the Writing of Human Gene Therapy Proposals*, (2000),
http://www.nhmrc.gov.au/publications/_files/gene.pdf
- Therapeutic Goods Administration, *Human Research Ethics Committees and the Therapeutic Goods Legislation*, (2001),
<http://www.tga.gov.au/docs/pdf/unapproved/hrec.pdf>
- *Prohibition of Human Cloning Act No. 144, An Act to prohibit human cloning and other unacceptable practices associated with reproductive technology, and for related purposes*, (2002), http://www.nhmrc.gov.au/publications/_files/prohibit.pdf
- Council of Australian Governments, *Arrangements for Nationally-Consistent Bans on Human Cloning and Other Unacceptable Practices, and Use of Excess Assisted Reproductive Technology (ART) Embryos*, (April 2002),
<http://www.coag.gov.au/meetings/050402/cloning.htm#2>
- National Health and Medical Research Council, *Ethical guidelines on the use of the assisted reproductive technology in clinical practice and research*, (September 2004),
http://www.nhmrc.gov.au/publications/_files/e56.pdf
- National Health and Medical Research Council, *Gene and related Therapies Research Advisory Panel (GTRAP)*, (2005),
<http://www.nhmrc.gov.au/about/committees/expert/gtrap/index.htm>

- Australian Government, *Legislation Review of Australia's Prohibition of Human Cloning Act 2002 and Research Involving Human Embryos Act 2002*, (August 2005), <http://www.lockhartreview.com.au/files/Legislation%20Review%20Reports%20Full%20Doc-19Dec05.pdf>
- Office of the Privacy Commissioner, *Review of the National Statement on Ethical Conduct in Research Involving Humans – Submission by the Office of the Privacy Commissioner to the National Health and Medical Research Council*, (2006), <http://www.privacy.gov.au/publications/nhmrcsub130406.pdf>
- Gene and Related Therapies Research Advisory Panel, www.nhmrc.gov.au/research/gtrap/about.htm

Descriptive Synopsis

Legislative acts:

The Australian government has banned germline therapy, making it an offense subject to criminal sanctions under the *Prohibition of Human Cloning Act* (Section 18). Any “human embryo that contains a human cell (within the meaning of Section 18) whose genome has been altered in such a way that the alteration is heritable by human descendants of the human whose cell was altered” is considered a “prohibited embryo” under this same Act (Section 22(4)).

In 2005 the Legislation Review Committee conducted an independent review of the provisions included in the Act in light of scientific progress and changes in community understanding and standards since 2002. In this report, the committee recommends that the implantation of an embryo carrying heritable alterations to its genome should remain prohibited. However, the creation of human embryos that have been genetically modified should be allowed, under license, for research, training and clinical purposes, as long as the embryo is not implanted into the body of a woman. The committee maintained that the current prohibition is problematic because “the ban on creating a human embryo with an altered genome prevents genetic manipulation of eggs, sperm or embryos to overcome genetic illness or disorder (or to enhance physical characteristics)...”

In 2002 the Council of Australian Governments (COAG) recognized the need for consistent legislation between the Commonwealth, States and Territories in Australia concerning medical and research practices. In the *Arrangements for Nationally-Consistent Bans on Human Cloning and Other Unacceptable Practices, and Use of Excess Assisted Reproductive Technology (ART) Embryos*, the council has agreed to enforce nationally consistent legislation banning the alteration of the genome of a human cell or in vitro embryo such that the alteration is inheritable (Section 2.5). The national legislation will be reviewed three years after taking effect in order to consider changes “in technology, the potential therapeutic uses of such technology and any changes in community standards” (Section 4).

Australia does not regulate somatic gene therapies specifically; however, the *Therapeutic Goods Act 1989* serves as a national system of control as concerns the quality, safety, efficacy, and timely availability of medicines, as well as for clinical trials. Under the Act, a “therapeutic good” is a broad term used to define “a good which is represented in any way to be, or is likely to be taken to be, for therapeutic use (unless specifically excluded or included under Section 7 of the *Therapeutic Goods Act 1989*).” Additionally, therapeutic use includes “use in or in connection with: preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury; testing the susceptibility of persons to a disease or ailment; replacement or modification of parts of the anatomy” (Section 3). Therefore, the Act regulates cell and tissue therapies by providing that all “devices of human, animal, bacterial or recombinant origin for use in, or on, the body of a person” must be included in the Australian Register of Therapeutic Goods. In order to be registered it is necessary to have pre-market approval and obtain a license from the Therapeutic Goods Administration (TGA), Australia’s regulatory agency for medical drugs and devices.

Other normative measures:

Proposals for gene therapy research in Australia are processed and reviewed at different stages by various ethics committees with different functions and roles. The initial phase of ethical and scientific review is done by an institutional Human Research Ethics Committee (HREC) to ensure that all proposals respect the form set out in the *Guidelines for Writing of Human Gene Therapy Proposals*, which have been adopted by the National Health and Medical Research Council (NHMRC). HREC then forwards the proposal to the Gene and related Therapies Research Advisory Panel (GTRAP), a sub-committee of the NHMRC’s Research Committee, for advice. The GTRAP reviews the ethical, scientific, technical, and medical issues related to the proposal and ensures that the gene therapy research conforms to the *Helsinki Declaration* and the NHMRC’s *National Statement on Ethical Conduct in Research Involving Humans 1999*. Additionally, for a complete assessment, the GTRAP may seek consultation from other bodies concerned with monitoring the safety of innovative genetic manipulation techniques (Office of the Gene Technology Regulator, OGTR) or the standards for product manufacture (Therapeutic Goods Administration, TGA, through the Clinical Trials Exemption process). Proposals that fall under the jurisdiction of the OGTR must also be submitted to the Institutional Biosafety Committee (IBC) for an initial assessment. For final approval, the HREC must ensure that the proposal has been approved by all relevant bodies and must also decide whether or not the research may proceed.

The GTRAP defines somatic cell gene therapy as “the introduction of DNA (deoxyribonucleic acid) or RNA (ribonucleic acid) into the somatic (non-reproductive) cells of humans, or the introduction into humans of cells whose genetic material has been modified, in order to provide an alternative form of treatment to improve the health of individuals.” According to the GTRAP, the insertion of DNA and RNA into germ cells or embryos is ethically unacceptable “since there is insufficient knowledge about the possible consequences including hazards and effects on future generations” (*Guidelines*

for Ethical Review of Research Proposals for Human Somatic Cell Gene Therapy and Related Therapies, 1999).

It should be noted that the NHMRC's *National Statement on Ethical Conduct in Research Involving Humans 1999* is currently being reviewed and until this process is finalized, the 1999 statement remains in force.

CANADA

- *Medical Devices Regulations – Part 3 – Medical Devices for Investigational Testing Involving Human Subjects (Food and Drugs Act), (1985),* <http://laws.justice.gc.ca/en/F-27/SOR-98-282/228654.html>
- *Food and Drug Regulations – Division 5 – Drugs for Clinical Trials Involving Human Subjects (Food and Drugs Act), (1985),* <http://laws.justice.gc.ca/en/f-27/c.r.c.-c.870/233981.html>
- Medical Research Council of Canada, *Guidelines for Research on Somatic Cell Gene Therapy in Humans*, (1990), p. 44.
- Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement — Ethical Conduct for Research Involving Humans*, (August 1998, amended 2000, 2002 and 2005), http://www.pre.ethics.gc.ca/english/pdf/TCPS%20October%202005_E.pdf
- Standing Committee on Health - House of Commons, *Assisted Human Reproduction: Building Families*, (2001), <http://www.parl.gc.ca/InfoComDoc/37/1/HEAL/Studies/Reports/healrp01/03-cov-e.htm>
- *An Act Respecting Assisted Human Reproduction and Related Research*, (March 2004), <http://laws.justice.gc.ca/en/A-13.4/text.html>

Descriptive Synopsis

Legislative acts:

According to the *Act Respecting Assisted Human Reproduction and Related Research 2004*, germline genetic alteration is banned and sanctioned by penal clauses (SS.5(1f) and 60). Under this Act, germline genetic alteration is defined as “altering the DNA of human sperm, eggs, or embryos such that the change can be transmitted to the person’s children and all generations to follow” (Section 3). Canadian legislation protects and preserves

“human individuality and diversity, and the integrity of the human genome” (Section 2), and therefore requires that any person who alters, manipulates, treats, or make use of an in vitro embryo must do so in accordance with regulations and have a license (Section 10(2)).

The *Food and Drugs Act 1985* includes two regulations which control human clinical trials and medical devices relating to investigational testing involving humans (*Medical Devices Regulations* and the *Food and Drug Regulations*). In the context of the *Food and Drugs Act 1985*, the term “clinical trials” includes “investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.” Somatic gene therapy research in Canada is still in its experimental stages and is not legislated specifically. However, all research involving somatic gene therapy may fall under the regulatory framework established by the above regulations.

Other normative measures:

The *Tri-Council Policy Statement*, adopted by the Medical Research Council, the Natural Sciences and Engineering Research Council, and the Social Sciences and Humanities Research Council of Canada, reiterates that gene alteration “remains experimental and is not ‘therapy’ in the accepted sense of the word” and “the use of animal models continues to be crucial in this area of incomplete knowledge.” Gene alteration in the context of the statement “involves the transfer in various vectors (or carriers) of genes into cells to induce an altered capacity of the cell... Alteration of human genes may be used to treat disease in an individual, alter germ cells to prevent disease or alter for cosmetic ‘improvement.’” Under Section 8.5 of this policy statement, gene alterations for therapeutic purposes that involve human somatic cells can be considered for approval but any gene alteration involving germline cells or human embryos is ethically unacceptable. Furthermore, Section 9.4 (b) adds that research involving human embryos may be ethically acceptable only “if the research does not involve the genetic alteration of human gametes or embryos.”

The Tri-Council expresses the following concerns regarding gene alteration outside the context of well-defined serious single-gene conditions or malignancies: (1) long-term follow-up of already treated individuals is not available, (2) the numbers of such individuals is small, and (3) the lack of information regarding long-term harms makes it inappropriate for such technology to be used for enhancement purposes or for non-life-threatening disorders.

The Standing Committee on Health of the House of Commons also agrees that germline genetic alteration should be banned due to safety concerns and possible unknown consequences for future generations (Section 5, *Assisted Human Reproduction: Building Families 2001*).

CHINA

- National People's Congress, *Drug Administration Law*, (1984, revised 2001).
- Ministry of Health and the State Drug Administration, *Guidance for New Drug Evaluation and Approval*, (1985, revised 1999).
- State Council, *Regulations for Implementation of the Drug Administration Law*, (1985, revised 2002).
- Ministry of Health, *Quality Control Guideline for Drug Manufacturing*, (1988, revised 1992 and 1998).
- Ministry of Health, *Guidelines on Ethical Review of Medical Research*, (1998).
- State Drug Administration and State Food and Drug Administration, *Quality Control Guideline for Nonclinical Drug Research*, (1999, revised 2003).
- State Drug Administration and State Food and Drug Administration, *Quality Control Guideline for Drug Clinical Trials*, (1999, revised 2003).
- State Food and Drug Administration, *Provisions for Drug Registration*, (2005).
- Yin, Hongzhang, *Regulations and Procedures for New Drug Evaluation and Approval in China*, (October 2006), 17 *Human Gene Therapy* 970-974.

Descriptive Synopsis

In China, a regulatory system governs clinical trials in humans and gene therapy products. The State Food and Drug Administration (SFDA), established in 2003 as a successor to the State Drug Administration (SDA), is the national regulatory authority responsible for the review and approval of clinical trial studies, drug registration, drug manufacturing and inspection, and licensing for drug importation. Based on the principles announced in the *Drug Administration Law* and its *Regulations*, the SFDA issued the *Provisions for Drug Registration 2005*, which applies to all registration of clinical trials. The *Provisions for Drug Registration 2005* also retained the clinical trials requirements that were promulgated in the 1985 and 1999 versions of the *Guidance for New Drug Evaluation and Approval*. At the regional level, each province has a provincial drug regulatory agency (provincial Food and Drug Administration, FDA), which is under the oversight of the SFDA. Each FDA is responsible for carrying out field inspections and ensuring that all drug clinical trials comply with statutory norms.

The evaluation and approval of new drugs in China follow a two-step process. The first step is the application and approval of the new drug clinical trial study and the second step is the registration approval for the manufacture of the new drug for market. It is required that all new drug developments complete preclinical studies before applying for approval for the clinical trial study. Preclinical studies for gene therapy products must comply with the *Points to Consider for Human Gene Therapy and Product Quality Control 2004* guidelines. For all clinical trials the following guidelines apply: *Quality Control Guideline for Drug Clinical Trials 1999/2003* (Good Clinical Practice, GCP), the *Quality Control Guideline for Drug Manufacturing 1988/1992 & 1998* (Good Manufacturing Practice, GMP) and the *Quality Control for Nonclinical Drug Research 1999/2003* (Good Laboratory Practice, GLP).

FRANCE

- National Consultative Bioethics Committee, *Opinion (No.22) on Gene Therapy*, (1990), <http://www.ccne-ethique.fr/english/start.htm>
- National Consultative Bioethics Committee, *Announcement on Gene Therapy*, (1991), 2:4 *Human Gene Therapy* p.329.
- *Code Civil*, (1994), http://ledroitcriminel.free.fr/la_legislation_criminelle/lois_speciales/code_civil.htm (certain extracts - in French)
- *Loi no. 94-654 du 29 juillet 1994 relative au don et à l'utilisation des éléments et produits du corps humain, à l'assistance médicale à la procréation et au diagnostic prénatal* (Law no. 94-654 governing the donation and use of elements and products of the human body, medically assisted reproduction, and prenatal diagnosis), (July 1994), <http://www.legifrance.gouv.fr/WAspad/UnTexteDeJorf?numjo=SPSX9400032L>
Revised by *Loi no. 2004-800 du 6 août 2004 relative à la bioéthique* (Bioethics Law), (August 2004), <http://www.legifrance.gouv.fr/WAspad/UnTexteDeJorf?numjo=SANX0100053L>
- Journal officiel de la République française, *Order of 23 February 2000*, (March 2000), No. 51, pp. 3234-3239.
- Journal officiel de la République française, *Decision of 24 July 2000 establishing a working group on controls of gene therapy products within the French Agency for the Health Safety of Health Products*, (August 2000), No. 183, p. 12344.

Descriptive Synopsis

Legislative acts:

In France, the *Law no.94-654 governing the donation and use of elements and products of the human body, medically assisted reproduction, and prenatal diagnosis* (1994), which was been amended in 2004 by the *Bioethics Law no.2004-800*, regulates gene therapy and gene therapy products. The new *Bioethics Law* established the French Biomedicine Agency, which is under the supervision of the Minister of Health and is responsible for quality assurance and ensuring ethical practices in biomedical research (Chapter VII of the law provides the organization, functions and mission of the agency).

Particular to cell and gene therapy research, the Biomedicine Agency collaborates with the French Health Products Safety Agency, which has the mandate to authorize and control the preparation, transformation, and use of human tissues and cells. The French Health Products Safety Agency was established in 1998. The *Decision of 24 July 2000* established a working group on control of gene therapy products within the French Health Products Safety Agency. This working group is responsible for specific tasks such as: (a) issuing, at the request of the the Director General of the French Health Products Safety Agency, an opinion on the laboratory controls necessary in the field of gene therapy, including controls associated with the quality and safety of products; (b) reflecting on the environmental conditions and infrastructures required in order to carry out these controls; and (c) providing, at the request of the Director-General, an opinion on any matter relating to quality controls of gene therapy products (Article 1 of the *Decision 2000*). The *Order of 23 February 2000* determines the criteria for authorization and notification with respect to the import and export of tissues and cells obtained from human tissues and gene and cell therapy products that are used for therapeutic purposes.

Chapter VI of the *Bioethics Law* regulates gene therapy and gene therapy products in particular. According to French law, gene therapy products cannot be manufactured, conserved, distributed, used for commercial purposes, imported, or exported unless authorization has been obtained. Any person who does not respect the provisions of the law is subject to criminal sanctions.

The *Bioethics Law* explicitly prohibits germline therapy and considers eugenic practices to be a crime against the human species. Furthermore, in order to protect biotechnology interventions, French law provides that processes of modification of the human genetic identity cannot be patented (Article 17).

The prohibition of germline therapy and eugenic practices in the *Bioethics Law* is consistent with what is prescribed in the *Civil Code*. The ban on eugenic practices and germline therapy ensures that Article 16(4) of the code, which explicitly protects the integrity of the human, is respected.

Other normative measures:

The National Consultative Bioethics Committee (Comité Consultatif National d'Éthique – CCNE) recommended in both its *Opinion on Gene Therapy 1990* and its *Announcement*

on *Gene Therapy 1991* that gene therapy be restricted to somatic cells. Deliberate modification of the genome of germinal cells should be formally prohibited. The committee stated that “there are serious misgivings about the practical implementation of this treatment: firstly, embryos cultivated in vitro would have to be analyzed to determine selection of those carrying the deficiency requiring correction, and it would be difficult to imagine re-implantation after gene therapy, since at the same time there would be embryos diagnosed as having no deficiency.” Regarding somatic gene therapy, the committee recommended that only “a specific genetic defect with serious pathological consequences for an individual can be considered for correction.” (The committee defined “somatic gene therapy” as “the modification of genetic capital concerning only non-reproductive cells in the body that would only affect an organ or a cell system,” while “germinal gene therapy” was defined as “a modification of the genetic capital of the reproductive cells (oocytes, spermatozoa and their precursors), which would lead to a change of an individual’s genome”).

GERMANY

- *The Embryo Protection Law*, (1990).
- German Working Group for Gene Therapy, *Guidelines for the Design and Implementation of Clinical Studies in Somatic Cell Therapy*, *J. Mol. Med.* (1995) 73(4): 207-11.
- German Medical Association, *Guidelines for Gene Transfer into Human Body Cells* (January 1995), <http://www.bundesaerztekammer.de/30/Richtlinien/Richtidx/Gentransfer.html> (in German)
- *The Drug Law* (Arzneimittelgesetz – AMG), (December 1998, consolidated text 2005), http://www.pei.de/cln_043/nn_432310/SharedDocs/Downloads/gesetze/arzneimittelgesetz.templateId=raw,property=publicationFile.pdf/arzneimittelgesetz.pdf (in German)
- German Society of Human Genetics, *Position Paper of the German Society of Human Genetics*, (2000), http://www.medgenetik.de/sonderdruck/en/Position_paper.pdf

Descriptive Synopsis

Legislative acts:

The artificial alteration of the human germline is criminalized by the *Embryo Protection Law* (art. 5, par. 1). Likewise, the law punishes anyone who uses or attempts to use a

human germ cell with artificially altered genetic information for fertilization (art. 5). Exceptions to this prohibition are possible if the germ line alteration is not the aim, but only a side effect of medical treatment. The pertinent article of the law reads as follows:

“Paragraph 1 (art. 5) does not apply to:

1. an artificial alteration of the genetic information of a germ cell situated outside the body, if any use of it for fertilization has been ruled out,
2. an artificial alteration of the genetic information of a different body’s germ line cell, that has been removed from a dead embryo, from a human being or from a deceased person, if it has ruled out that
 - a) they will be transferred to an embryo, fetus or human being or
 - b) a germ cell will originate from them, and likewise
3. inoculation, radiation, chemotherapeutic or other treatment by which an alteration of the genetic information of germ line cells is not intended.”

For the purposes of the *Embryo Protection Law*, germ line cells “are all cells that lead from the egg and sperm cells to the resultant human being and, further, the egg cell from capture or penetration of the sperm cell until the ending of fertilization by fusion of the nuclei.” In addition, the term “embryo” has been defined as a “human egg cell, fertilized and capable of development, from the time of fusion of the nuclei, as well as each totipotent cell removed from an embryo that is capable, in the presence of other necessary conditions, of dividing and developing into an individual.”

Gene therapy and somatic cell therapy products used in or on humans (in vivo) are termed gene transfer medicinal products (GT-MPs). They are medicinal products (drugs) according to Section 2 (1) of the *German Drug Law* (AMG) and include DNA, viral or non-viral vectors and genetically modified autologous, allogeneic or xenogeneic cells (used in vivo). No official definition of GT-MPs is given in the AMG. GT-MPs are either vaccines, blood products, or other drugs, according to Section 4 (4) and Section 4 (2) of the AMG. According to Section 77 of the AMG, the Paul-Ehrlich-Institute, Langen, is the competent higher authority for those GT-MPs which are vaccines and blood products, whereas the Federal Institute for Drugs and Medical Devices (BfArM, Bonn) is the competent higher authority for other GT-MPs.

As for other medicinal products, regulations relevant to the manufacture and clinical trial of GT-MPs are provided by the AMG and the professional law of physicians. In contrast to other medicinal products, an appraisal of the central Commission Somatic Gene Therapy of the Scientific Board of the German Medical Association is required for clinical trials involving the use of GT-MPs

<http://www.bundesaerztekammer.de/30/Ethik/80Themen/85KomSomGen/>).

Prior to licensing, gene transfer medicinal products are to be used in or on humans during clinical trials only (according to the appraisal of the Kommission Somatische Gentherapie’ der Bundesärztekammer; (KSG-BÄK)). Very few exceptions require special consideration by the KSG-BÄK. The *Guidelines for Gene Transfer into Human Body Cells* published by the German Medical Association specify the necessary ethical

considerations and are guidelines for clinical trial applications. Clinical trials can only be conducted if certain requirements are met (see Sections 40 & 41 of the AMG).

The Federal Institute for Drugs and Medical Devices (BfArM) is an independent higher federal authority within the portfolio of the Federal Ministry of Health. The main tasks of the BfArM are licensing and registration of medicinal products, authorization of clinical trials, and recording and assessment of risks associated with medicinal products and medical devices, as well as control of the (legal) trade with narcotic drugs. The BfArM is involved in the development of regulatory and scientific standards and guidelines. It also provides scientific advice for government authorities and information for expert groups and the general public.

The Research Council is the most important research-related BfArM body. It is involved in continuing development of research concepts and their transfer into practice. The council evaluates the applications for research projects and devises the basic procedures for research organizations. The final decision regarding the recommendations given by the council is made by the head of BfArM. The council was appointed by the Federal Ministry of Health in late 2003 and formally constituted in 2004.

(Please refer to: Paul-Ehrlich-Institut. *Regulation of Gene Transfer Medicinal Products in Germany*, http://www.pei.de/cln_043/nn_437232/EN/infos-en/fachkreise-en/genther-fach-en/regulation-genther-en.html#doc437284bodyText6)

Other normative measures:

Due to the promise for discovering cures for diseases and decreasing human suffering, the German Society of Human Genetics recommends that somatic gene therapy be promoted. In its *Position Paper*, the society adds that, “before such a gene therapy is used, the usual requirements for medical treatments must be met and the patient must be counseled beforehand.” However, the society does not support the development and use of gene therapy procedures for non-therapeutic purposes. The society considers germline therapy to be a “genetic manipulation of embryonal cells after an in vitro fertilization with the goal of producing a human individual without a certain genetically determined disorder,” a prohibited act. Germline therapy is therefore not a medical treatment for patients but an experiment, “a basic hypothesis of which is to be verified or refuted by a human existence.” The society further adds that, “currently and in the near future, reasonable and responsible application of these techniques is not foreseeable because of technical and ethical problems.”

INDIA

- *Drugs and Cosmetics Act*, (1940, amended 2003), <http://indianmedicine.nic.in/html/pharma/adrugsnoti.pdf>

- Indian Council of Medical Research, *Consultative Document on Ethical Guidelines for Biomedical Research on Human Subjects*, (2000), <http://icmr.nic.in/ethical.pdf>
- Indian Council of Medical Research, *Statement on Specific Principles on Human Genetics Research*, (July 2000), <http://www.icmr.nic.in/ethical.pdf>
- Department of Biotechnology, Ministry of Science and Technology, Government of India, *Ethical Policies on the Human Genome, Genetic Research and Services*, (June 2001), <http://dbtindia.nic.in/publication/publicmain.html>
- Ministry of Health, *Good Clinical Practices (GCP)*, (2001), <http://unpan1.un.org/intradoc/groups/public/documents/APCITY/UNPAN009867.pdf>
- Indian Council of Medical Research and the Department of Biotechnology, *Draft Guidelines for Stem Cell Research and Therapy*, (2006), http://www.icmr.nic.in/stem_cell/Stem_cell_guidelines.pdf
- Indian Council of Medical Research, *Guidelines for preparing Standard Operating Procedures (SOP) for Institutional Ethics Committee for Human Research*, http://www.icmr.nic.in/ethics_SOP.pdf

Descriptive Synopsis

Although there is no specific legislation in India governing gene therapy, the Indian Council of Medical Research (ICMR) states that gene therapy should be subject to ethical codes that apply to research involving human patients. Therefore, the regulation of gene therapy can be covered by the same regulations that control clinical trials or human experimentation. Clinical trials in India are minimally regulated by the *Drugs and Cosmetics Act 1940, amended 2003*, and must also comply with the *Ethical Guidelines for Biomedical Research on Human Subjects 2000* (adopted by the Indian Council of Medical Research, ICMR) and the *Good Clinical Practices (GCP) 2001* guidelines (adopted by the Ministry of Health). All research proposals for human trials must be approved by an Institutional Ethics Committee (IEC) and must obtain consent from research subjects. Accordingly, each IEC must respect the standard operating procedures stipulated by the ICMR guidelines.

The ICMR states that, as a human genetic research practice, gene therapy would help alleviate human suffering. According to the council, somatic cell gene therapy is “the only method that may be permissible for the purpose of preventing or treating a serious disease when it is the only therapeutic option.” (*Statement on Specific Principles on Human Genetic Research 2000*). The council adds that somatic gene therapy should be restricted to the alleviation of life threatening or seriously disabling genetic diseases in individual patients and should not be allowed for the purpose of changing normal human traits. Ethical review of gene therapy in India is divided into two stages. The first phase is the evaluation of the procedure by the National Bioethics Committee under the

Department of Biotechnology (DBT) and the second phase is obtaining clearance by the local IEC and Central Ethical Committee (CEC) of the ICMR. The ICMR believes that it is ethical for children to be candidates for gene therapy if the therapy is meant for a childhood disorder.

Germline therapy, gene therapy for enhancement and eugenic genetic engineering are all banned by the ICMR. In particular, the ICMR states that there is insufficient knowledge at the present time concerning the effects of the attempts to “alter/enhance the genetic machinery of humans,” and that, “the influence of environmental interaction on the expression of genetic characters is poorly understood,” (*Statement on Specific Principles on Human Genetics Research 2000*).

Under the *Ethical Policies on the Human Genome, Genetic Research and Services 2001*, the Department of Biotechnology, the Ministry of Science and Technology and the Government of India all agree that somatic cell gene therapy be allowed “with appropriate safety measures” and “when it is the only therapeutic option” or “it is indisputably considered superior to other existing options.” The policies also ban germline therapy in humans.

In 2006, the ICMR and the Department of Biotechnology drafted *Guidelines for Stem Cell Research and Therapy*. Under these guidelines, any research either related to germline genetic engineering or involving implantation of a human embryo into a uterus after in vitro manipulation at any stage of development is prohibited (Section 6.3.1 & 6.3.4).

ISRAEL

- *Human Experimentation Regulations*, (1980).
- *Pharmacists Regulations*, (1986).
- *Patient’s Rights Act*, (1996), Official Gazette, Statutes, no. 1591, p.327, <http://waml.haifa.ac.il/index/reference/legislation/israel/israel1.htm>
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- *Public Health (Extra-Corporeal Fertilization) Regulations*, (1997).
- Ministry of Health, Pharmaceutical Administration, *Guidelines for Clinical Trials in Human Subjects*, (1999).
- *Genetic Information Act*, (2000), Official Gazette, Statutes, no.1766.

- Ministry of Health, Pharmaceutical Administration, *Guidelines for the submission of a request to include in a pharmaceutical product in the national list of health services*, (2004), http://www.health.gov.il/download/forms/a28_aclalaeng2002.doc
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- Israel Drug Registry, <http://www.health.gov.il/units/pharmacy/trufot/index.asp?safe=e>
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- Frenkel, Ran, Mina Arnos, Hanna Bilig, et. al., *Regulation of Clinical Trials in Israel: Recent Developments*, (2000) 34 Drug Information Journal 847-854.

Descriptive Synopsis

In 1999, the Israel government adopted the *Prohibition of Genetic Interventions (Human Cloning and Genetic Modification of Reproductive Cells) Act* to prescribe a five-year period during which certain genetic interventions on humans are banned in order to allow assessment of the moral, social, legal and scientific repercussions of such interventions and their impact on human dignity. The Act was renewed in 2004 and will be in force until 2009. Under this Act, germline gene therapy is considered to be a genetic intervention that is banned (Section 3(1)). In particular, the Act states that, “no person shall...us[e] reproductive cells that have undergone a permanent intentional genetic modification (germ line gene therapy) in order to cause the creation of a person.” However, notwithstanding the prohibited practices, the Minister of Health may permit through regulations certain kinds of genetic intervention provided that human dignity is not compromised and that the advisory committee grants a favorable recommendation (Section 5). The Act has named the Supreme Helsinki Committee for Genetic Medical Experiments on Humans (established under the *Public Health Regulations 1997*) as the advisory board with the mandate to “follow developments in medicine, science, biotechnology, bioethics and law in the field of genetic experimentation on human beings in Israel and abroad,” (Sections 2 and 4(a)(1)).

Israel does not have any laws or guidelines regulating somatic gene therapy in particular as it is considered to be still in the experimental stages. However, there exist legislative acts and normative measures that govern biomedical experimentation or clinical trials on

humans. In 1996 the *Patient's Rights Act* was adopted in order to incorporate provisions regarding informed consent, quality control and ethics committees, and the safeguard of patient's rights in medical facilities. The provisions in this Act may be relevant to human biomedical research or human experimentation in clinical settings.

The *Guidelines for Clinical Trials in Human Subjects 1999* (adopted by the Pharmaceutical Division of the Ministry of Health) and the *Human Experimentation Regulations 1980* provide the regulatory process for human clinical studies. Each research protocol must be submitted to the relevant institutional review board (IRB) and then approved by the Minister of Health. In 2000 the Minister of Health appointed the Supreme Helsinki Committee for Genetic Medical Experiments on Humans to be the highest regulatory body in the field of human genetic research. Major sources of normative guidance for the Supreme Helsinki Committee are the *Genetic Information Act 2000* and the *Helsinki Declaration*, which provide substantive standards for biomedical research in humans. The *Pharmaceutical Regulations 1986* mandates that drugs cannot be manufactured, marketed, imported and authorized for use unless registered on the Israel Drug Registry, which is controlled by the Minister of Health.

JAPAN

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hospitals, and medical schools, (2006), 12:9 Medical Science Monitor 7-15,
http://www.medscimonit.com/pub/vol_12/no_9/8724.pdf

Descriptive Synopsis

Legislative acts:

The Japanese law regulating human cloning and other techniques (2001) states that any technique that manipulates embryos or germ cells of a human could “have severe influence on the preservation of human dignity, safety for human life and body, and maintenance of social order,” (Article 1).

Other normative measures:

Since the early 1990s government agencies in Japan have introduced a series of guidelines for gene therapy clinical trials. In the *Guidelines for Genetic Testing*, adopted in 2004 by ten genetic-medicine-related societies, the term “gene therapy” is used to refer to “a technique where a foreign gene, either as is or incorporated into a vector (a carrier), is introduced into the body to elicit the synthesis of a desired protein in the target cell or tissue for therapeutic purposes.” The National Institute of Health Science of Japan defines gene therapy as, “to administer genes or genetically modified cells to the subject for treatment of diseases.” The National Institute of Health bans germline gene therapy explicitly in their report *Current Status of Gene Therapy Products in Japan*.

In 1994 the Ministry of Health, Labor and Welfare (MHW) released the first version of the *Guidelines for Clinical Research on Gene Therapy*. The purpose of these guidelines is to “ensure scientific justifiability of the efficiency and safety of such [gene therapy] studies, as well as to be sufficiently sensitive to the ethical aspects of such studies.” The following main topics are covered in the guidelines: the definition of gene therapy, diseases targeted by gene therapy, prohibition of transferring genes into the human body except for treatment purposes, prohibition of genetic alteration of germ cells, ensuring the effectiveness and safety of gene therapy, protection of public health, informed consent, and procedures for conducting gene therapy. Under these guidelines, gene therapy is limited to somatic cells and is recommended only for terminal illnesses for which there is no existing remedy. The guidelines provide that all research protocols must be approved by the institutional review board before being submitted to the MHW for approval.

Shortly after the adoption of the 1994 guidelines, the MHW and the Ministry of Education, Culture, Sports, Science and Technology (MESC) formed a joint working group to examine the safety and efficacy of gene therapy trials. In 1995, the MHW adopted the *Guidelines for the Assurance of the Quality and Safety of Therapeutic Materials for Gene Therapy*. The Japan Society of Gene Therapy was established in that same year to facilitate interdisciplinary gene therapy research..

In 2002, the MHW and MESC jointly publicized the revised guidelines on gene therapy. There are no substantive changes in the 2002 version except changes to the regulatory process, which simplify and facilitate the process. Research protocols must still be initially approved by the institutional review board (IRB) or the ethics committee (EC) to ensure that they meet ethical standards delineated by guidelines. The IRB or EC must then file the protocol with both the MHW (responsible for ensuring the social and ethical aspects of the trial) and the MESC (responsible for the scientific aspect of the trial).

MEXICO

- *General Health Law of 7 February 1984*, (amended 2006),
<http://www.diputados.gob.mx/LeyesBiblio/pdf/142.pdf> (in Spanish)
- *Regulation of the General Health Law on the Sanitary Control of Organs, Tissues and Human Cadavers*, (1985),
<http://www.salud.gob.mx/unidades/cdi/nom/compi/rlgsmcsdotcsh.html> (in Spanish)
- *Regulation of the General Health Law on Scientific Research*, (1987),
http://www.respyn.uanl.mx/iv/3/contexto/reglamento_investigacion.htm (in Spanish)
- *Penal Code of Mexico's Federal District*, (2002),
<http://www.df.gob.mx/leyes/normatividad.html?materia=1&apartado=16&disp=394> (in Spanish)
- *Regulation on the System for National Researchers*, (2006),
<http://www.diputados.gob.mx/LeyesBiblio/regla/n324.pdf> (in Spanish)

Descriptive Synopsis

Mexican federal legislation does not regulate explicitly human genetic modification. The *General Health Law* (GHL) and its *Regulation on Scientific Research* (RSR) and *Regulation on the Sanitary Control of Organs, Tissues and Human Cadavers* (RCOTHC), have been interpreted as implicitly prohibiting human germline modification. The article on which this interpretation is based stipulates that research on embryos can only be conducted for the benefit of the embryo and then only when their “security/integrity is guaranteed,” (Art. 56). For the purpose of this law, an embryo is “the product of conception from fertilization to the end of the 12th week of gestation” (Art. 314). This definition is consistent with the Regulation of the General Health Law on Scientific Research, which retains the same definition for an embryo in its Article 40.

The aforementioned legislation regulates the use of human cells (including germinal and somatic cells) and embryos, and entrusts the Secretary of Health with the granting of

licenses and establishing sanitary control measures for their donation and use (whether for clinical application or research purposes) (Art. 313 GHL).

The only legal norm contemplating human genetic modification is the Penal Code for the Mexican Federal District (CPDF). According to article 154 of the CPDF, the crime of “genetic manipulation” is committed when a person (i) “with a purpose other than eliminating or diminishing serious diseases or disorders manipulates human genes in such a way that alters a genotype; (ii) fertilizes a human egg with a different purpose than human procreation; or (iii) creates human beings by cloning or performs genetic engineering with illicit purposes” (author’s translation) (Art. 154). The disposition of germinal cells is considered to be illicit when it is performed against the purposes for which the donor(s) has granted authorization (Art. 149). Hence, the CPDF does not prohibit performing human genetic modification or conducting scientific research in this area, unless it is done for non-therapeutic purposes. Furthermore, Art. 155 of the same code establishes that if a child is born in contravention of the abovementioned provisions, the compensation of damages includes the payment of child support to the mother.

These provisions create potential conflicts in terms of jurisdiction since the CPDF – whose jurisdiction is limited to Mexico – regulates and sanctions the same conducts and practices already covered by federal sanitary legislation. Thus, the framework for the interpretation of the CPDF must be the General Health Law and its regulations. These norms do not specify for what uses donors of cells, organs and tissues can grant authorization, but do impose certain limits for the use of eggs and sperm by requiring the donor’s informed consent and prohibiting the commercialization of germinal cells (Art. 327 LGS, Art. 56 RCOTHC).

There is no specific federal or local legislation dealing with somatic human modification or gene therapy; hence it is governed by the general provisions related to human experimentation and scientific research (Arts. 100 and 465GHL, Arts. 13 and 14RSR). These provisions encompass the internationally accepted safeguards for human scientific research (Declaration of Helsinki, Belmont Report).

Several bills that would ban human germline interventions that have no therapeutic purpose have been introduced in both parliamentary chambers and are currently under debate.

THE NETHERLANDS

- *Medicines Act*
- Health Council of the Netherlands, Committee on Genetic Testing and Gene Therapy, *Heredity: Science and Society – On the Possibilities and Limits of Genetic Testing and Gene Therapy*, (1989), The Hague: Health Council of the Netherlands, 29 December 1989, p.196.

- Council of Europe, *Convention on Human Rights and Biomedicine*, (1997), <http://www.oup.co.uk/pdf/bt/cassese/cases/part3/ch16/1121.pdf>
- Health Council of the Netherlands, *Gene Therapy*, (1997), <http://www.gr.nl/adviezen.php>
- *The Medical Research Involving Human Subjects Act (WMO)*, (1999), <http://www.healthlaw.nl/humsub.pdf>
- *Decree on Centralised Medical Ethics Review of Protocols for Medical Research Involving Human Subjects*, (1999).
- *Central Review of Medical Research Involving Human Subjects Decree*, (1999).
- Netherlands Government, Central Committee on Research Involving Human Subjects, *Statement on Gene Therapy* (in Dutch), (2001).
- *Decree on Immunological Pharmaceutical Products*, (2001).
- *Act containing rules relating to the use of gametes and embryos (Embryos Act)*, (September 2002), http://www.minvws.nl/images/eng-embryowettekst_tcm20-107819.pdf
- Central Committee for Research Involving Human Subjects, *Manual for the Review of Medical Research Involving Human Subjects*, (2002), http://www.ccmo-online.nl/hipe/uploads/downloads_catp/Toetsingshandleiding-2002_ENG.pdf
- Central Committee for Research Involving Human Subjects, *Guidelines for Researchers on the Evaluation by Official Agencies of Gene Therapy Research*, (2004), <http://213.154.234.72/Documenten/Documenten%20IM/LeidraadGetherapieversie1-10-2004.pdf> (in Dutch)
- Ministry of Health, Welfare and Sports, *Clinical Research with medicinal products in the Netherlands (Instruction Manual)*, (2005), http://www.ccmo-online.nl/hipe/uploads/downloads_cati/Instruction%20manual%20versie%202.pdf

Descriptive Synopsis

Legislative acts:

The *Embryos Act* prohibits and criminalizes any “intentiona[l] modif[ication] [of] the gene material of the nucleus of human germ-line cells with which pregnancy is to be indicated,” (Section 24(g) and 28(1)).

Although there are no specific laws governing somatic gene therapy in particular, the *Medical Research Involving Human Subjects (MWO) Act 1999* was enacted to protect subjects who participate in medical research studies by creating a regulatory process to examine all medical research. The Act established the Central Committee for Medical Research Involving Human Subjects (CCMO) with the mandate to approve medical research protocols involving human subjects. In the Netherlands, medical research involving humans may only be performed if a recognized review committee has approved the protocol. These review committees are overseen by the CCMO, which recognizes and monitors the work of the review committees. The Act applies to all medical research in which humans are subject to treatments. The term “medical research” includes intervention research that examines the working mechanisms of the human body and the therapeutic effects of an intervention.

In 2002 the CCMO published the *Manual for the Review of Medical Research Involving Human Subjects*, a practical guide containing an overview of the rules governing accredited medical ethics review committees. The document makes reference to the *Guidelines for Good Clinical Practice 1993* (published by the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use). The *Good Clinical Practice Guidelines* do not have binding force but are integrated into Dutch law by Article 55 of the *Decree on Manufacturing and Delivering Medicinal Products*, issued pursuant to the *Medicines Act*. Art. 55 states that a “medicinal product trial involving human subjects must be organised in accordance with the Guidelines for Good Practice.”

The MWO Act has resulted in the adoption of several different decrees. The *Decree on Centralised Medical Ethics Review of Protocols for Medical Research Involving Human Subjects* stipulates that all gene therapy research protocols must be reviewed by the central committee. The *Central Review of Medical Research Involving Human Subjects Decree* at Section 1 states that “research protocol for the following types of medical research shall require the approval of the central committee referred to in Section 14 of the *Medical Research Involving Human Subjects Act*: a) medical research in which intentional alterations to the genetic material in human-body cells are made...”

In March 2006 the MWO Act was revised in order to incorporate requirements as described in the European Union directive *Good Clinical Practice*. Major changes in the Act concern clinical trials with medicinal products. The Ministry of Health, Welfare and Sports has published an *Instruction Manual* which describes the process for submission and execution of new medicinal product trials. Section 1.1 of the manual states that all clinical research protocols must be reviewed by the Competent Authority (CA), either the accredited Ethics Committee or the CCMO.

(The Dutch version of the revised MWO Act is available online at: http://www.ccmo-online.nl/hipe/uploads/downloads_catw/WMO%20per%201%20maart%202006.pdf)

Other normative measures:

The Health Council of the Netherlands recommends in its *Gene Therapy* report that there should be increased research in the field of gene transfer and gene expression, while ensuring the importance of “prudence, openness and realism in reporting the advances in somatic gene therapy research.” According to the council, somatic gene therapy consists of “introduction of specific alterations in the genetic material of human body cells for the purposes of medical treatment, diagnosis or disease prevention...” For clinical researchers working with gene therapy, the council recommends that clinical protocols should respect high standards of excellence consistent with the principles of Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP). The council further recommends that licensing of gene therapy providers be approved only if applicants possess the required expertise and infrastructure for the specific protocol in question.

The Netherlands is a signatory of the 1997 European *Convention on Human Rights and Biomedicine*, which protects the human integrity and human rights of all research subjects in biology and medicine.

SOUTH AFRICA

- Minister of Health, *Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa*, (2000).
- Medical Research Council of South Africa, *Guidelines on Ethics for Medical Research: Reproductive Biology and Genetic Research*, (2002), <http://www.sahealthinfo.org/ethics/book2.htm>
- *National Health Act*, (2003), http://www.parliament.gov.za/pls/portal/web_app.utl_output_doc?p_table=acts&p_doc_col=act doc&p_mime_col=mime type&p_id=606077
- Minister of Health, *Ethics in Health Research: Principles, Structures and Processes, Research Ethics Guidelines*, (2004), <http://www.doh.gov.za/docs/ethnics-f.html>

Descriptive Synopsis

Legislative acts:

In South Africa, human genetic modification technologies are regulated by the *National Health Act* and the ethics research guidelines issued by the Minister of Health. Under the *Act*, “the manipulation of any genetic material, including human gametes, zygotes or embryos” is explicitly prohibited. Violation of the ban is punishable with imprisonment for up to five years and/or the imposition of fines (Art. 62).

With regard to somatic gene therapy, the general provisions pertaining to research on human subjects are applicable (*National Health Act*, Chapter 9). The National Health Research Ethics Council is responsible for the drafting of guidelines for the functioning of research ethics committees and for the setting of norms and standards for conducting research and clinical trials on humans.

Finally, the Minister of Health's "Ethics in Health Research" guidelines contain South Africa's national policy on the ethical practice of research. They establish mechanisms for the ethical review of studies conducted on human subjects and draw attention to the ethical implications of professional actions, particularly human genetic research.

Other normative measures:

The Medical Research Council (MRC) of South Africa, in its 2002 *Guidelines on Ethics for Medical Research*, adopted recommendations for the regulation of human genetic modification techniques. The MRC is of the opinion that human germline modification should not be attempted at this time due to the insufficient knowledge about possible risks to future generations.

Relating to somatic cell gene therapy, the MRC is of the opinion that it should be governed initially by the same requirements that already apply in South Africa to other research involving human subjects. Given the uncertainty about its safety and efficacy, the MRC recommends that somatic gene therapy be limited to patients in whom the potential for benefit is greatest in relation to possible inadvertent harm (i.e. patients whose disorders are life threatening or cause serious handicap and/or those for which other treatment is unavailable or unsatisfactory).

Finally, the MRC recommends that a new expert supervisory body be established with the responsibility for:

- a) advising on the content of proposals, including the details of protocols, for therapeutic research in somatic cell gene modification;
- b) advising on the design and conduct of the research;
- c) advising on the facilities and service arrangements necessary for the proper conduct of the research;
- d) advising on the arrangements necessary for the long-term surveillance and follow-up of treated patients; and,
- e) receiving proposals from clinicians who wish to conduct gene therapy in individual patients, and making an assessment of:
 - the clinical status of the patient;
 - the scientific quality of the proposal, with particular regard to the technical competence and scientific requirements for achieving therapy effectively and safely;
 - whether the clinical course of the particular disorder is known sufficiently well for sound information, counseling and advice to be given to the patient (or those acting on behalf of the patient) so that informed consent

may be obtained (see 5.3 Book 1) - for the outcomes of therapy to be assessable;

- the potential benefits and risks to the patient of the proposal; and,
- the ethical acceptability of the proposal.

In the light of this assessment, the expert supervisory body should recommend whether or not the proposal should be approved. Where applicable, conditions should be stated. The supervisory body should also have responsibility for:

- f) acting in collaboration with existing Research Ethics Committees;
- g) acting as a repository of up-to-date information on research in gene therapy internationally;
- h) setting up and maintaining a confidential register of patients who have been the subjects of gene therapy;
- i) oversight and monitoring of the research; and,
- j) providing advice to Health Ministers on scientific and medical developments that bear on the safety and efficacy of human gene modification.

SOUTH KOREA

- Ministry of Health and Welfare, *Guidelines on the Safety of Biotechnology Research*, (2000).
- *Bioethics and Biosafety Act*, (2005), <http://www.koreabioethics.net/5-2/7.doc>

Descriptive Synopsis

In South Korea, the *Bioethics and Biosafety Act* establishes the regulatory process for biomedical practices and includes provisions regulating gene therapy. This Act interprets gene therapy as “procedures involving genetic mutation that are intended to prevent or treat certain diseases,” (Art. 2). South Korea does not allow gene therapy for all purposes but limits the practice to the specific cases listed in Article 36 of the Act. The particular cases include:

1. To treat or cure genetic disorders, cancer, Acquired Immune Deficiency Syndrome, and other life threatening or seriously damaging diseases;
2. To treat diseases for which there currently is no cure or when the expected results of gene therapy outweigh those of other therapies; or
3. To prevent or cure diseases that the Minister of Health and Welfare, after a review by its board, targets for gene therapy treatment.

The Act created the National Bioethics Committee in Korea, which is responsible, under the authority of the President of South Korea, for ensuring that ethical and safety standards are respected in all research relating to life sciences and biotechnologies. The

Bioethics Committee also has the authority, under Article 6(5) of the Act, to determine the types of diseases for which gene therapy may be performed under Article 36(3) of the Act. If the particular case allows for gene therapy research, all institutions wishing to conduct gene therapy must first register with the Ministry of Health and Welfare (Article 37). Penal clauses exist which sanction any infringements to the Act.

The Act prohibits any gene therapy on sperm, oocytes, embryos, or foetuses. The Ministry of Health and Welfare's *Guidelines on the Safety of Biotechnology Research* also explicitly prohibit the manipulation of human germlines.

SINGAPORE

- *Medicines Act* (Section 74, Cap. 175), (1975), <http://statutes.agc.gov.sg>
- *Medicines (Clinical Trials) Regulations*, (1978, amended 2000).
- National Medical Ethics Committee, *Singapore Guideline for Good Clinical Practice*, (1998).
- National Medical Ethics Committee, *Ethical Guidelines for Gene Technology*, (2001), <http://www.moh.gov.sg/cmaweb/attachments/publication/3352285aef1r/GeneGuidelines.pdf>
- Bioethics Advisory Committee of Singapore, *Advancing the Framework of Ethics Governance for Human Research*, (2003), <http://www.bioethics-singapore.org/resources/pdf/Annexe%20B%20-%20CP.pdf>
- Bioethics Advisory Committee of Singapore, *Research Involving Human Subjects: Guidelines for IRBs*, (2004), <http://www.bioethics-singapore.org/resources/reports3.html>

Descriptive Synopsis

In Singapore, no laws exist that regulate gene therapy explicitly; however, there is a regulatory system in place for ethical governance of clinical trials. Concerning drug trials, three main legislations provide the current formal regulatory framework: the *Medicines Act 1975*, the *Medicines (Clinical Trials) Regulations 1978*, and the *Singapore Guidelines for Good Clinical Practice (SGGCP) 1998*.

The *Medicines Act* and subsequent *Clinical Trials Regulations* regulate the conduct of clinical trials and set out the procedures and conditions of obtaining a license to practice. Before licensing approval, all clinical protocols are subject to an independent review carried out by the institutional review board (IRB). All protocols must comply with the

Singapore Guidelines of Good Clinical Practice 1998, which were adopted in order to implement the principles of the *Helsinki Declaration* into Singaporean law. If the protocol is approved by the IRB, the proposal is then submitted to the Health Science Authority (HSA), the statutory licensing board of the Ministry of Health (MOH) charged with ensuring the quality, safety, and efficacy of medicines, medical devices, radiation equipment, blood and its products, and all health-related products available in Singapore. The HSA is responsible for providing comprehensive regulatory services for the evaluation and marketing approval of therapeutic products. The Medical Clinical Research Committee (MCRC) of the HSA is responsible for reviewing applications for drug trials. The MCRC is aided by the Centre for Pharmaceutical Administration (CPA) of the HAS. (The responsibilities, composition, functions and operations of the MCRC are detailed in Article 3.1 of the SGGCP, and those of the IRB in Article 3.2 of the SGGCP).

It is important to note that the term “clinical trial” in the context of the *Medicines Act* and the *Clinical Trials Regulations* applies only to pharmaceutical drug trials and has no application to other research or trials involving human subjects or human biological materials. However, the SGGCP defines the clinical trial or clinical study as “any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining the safety and/or its efficacy,” (Article 1.12 of the SGGCP).

For clinical research other than drug trials, three main committees have been created to provide bioethical infrastructure for human research. In 1994, the MOH established the National Medical Ethics Committee (NMEC); The NMEC is a national policy advisory board which provides guidance regarding ethical issues in medical practice. The NMEC has adopted several guidelines, including the *Ethical Guidelines on Research Involving Human Subjects 1997* and the *Ethical Guidelines for Gene Technology* (which is reviewed further in the present report). In 1998, the MOH announced the acceptance of the NMEC’s *Ethical Guidelines on Research Involving Human Subjects 1997* and required that all the IRB’s from public or restructured hospitals comply with the established guidelines.

In June 2000 the Ministerial Committee for Life Sciences was created in order to oversee all development of biomedical sciences in Singapore. The Committee for Life Sciences covers various aspects of education, research and development, and industry development in the field of biotechnology. The Committee for Life Sciences collaborates with the Bioethics Advisory Committee (BAC), which was created in December 2000. The BAC was appointed by the Singaporean government to study “the legal, ethical and social issues arising from biomedical sciences research.” The BAC focuses on the ethical implications of research rather than the implications of clinical settings and recommends policies to the Committee for Life Sciences. The BAC has published several reports (the *Advancing the Framework of Ethics Governance for Human Research 2003* and the *Research Involving Human Subjects: Guidelines for IRBs 2004*) which examine the

current system of ethical governance in Singapore, provide recommendations on the constitution and roles of the IRB's in the context of clinical research, and to provide recommendations regarding future development of Singapore's ethical governance of clinical research.

Other normative measures:

In 2001 the National Medical Ethics Committee of Singapore published the *Ethical Guidelines for Gene Technology*, which provides comprehensive recommendations regarding somatic gene therapy and germline gene therapy.

The committee defines "gene therapy" as "the administration of nucleic acids to living systems with the intention to use the expression products of these nucleic acids for therapeutic purposes" where "the expression of the transferred genes is essential for successful gene therapy," (Section 5.2). The committee supports somatic gene therapy but recommends that germline gene therapy not be permitted.

The committee defines somatic gene therapy as the correction of the genetic defects in postnatal somatic cells in the body. The committee states that somatic gene therapy is fundamentally not different from any form of organ transplantation, blood cell transfusion or experimental treatment (Section 8.1). It recommends the following concerning gene therapy, or somatic gene therapy:

- a. rigorous peer review of research protocols on application of gene technology should be mandatory to ensure that proposed studies are scientifically sound and well-designed to address specific hypotheses, with well-defined and valid molecular, biochemical and/or quantitative clinical endpoints;
- b. gene therapy must be evaluated through rigorous clinical studies before clinical adoption;
- c. informed consent must be obtained for the performance of clinical gene therapy;
- d. gene therapy is permissible in subjects who do not have end-stage illness (risks, benefits and alternative (i.e. non-gene) therapy options must be fully considered first);
- e. gene therapy in humans should be confined to alleviating disease in individual patients (gene therapy to enhance or change normal traits is strictly prohibited);
- f. somatic gene therapy should be deferred till the last semester of pregnancy or postpartum unless the perceived benefits to the mother clearly outweigh the risks for the fetus;
- g. gene therapy protocols should follow subjects indefinitely;
- h. human gene therapy should receive the same scrutiny in peer review as other applications for experimental therapies; and,
- i. there should be a concerted effort on the part of scientists, clinicians, science writers, research institutions, and the press to inform the public regarding not only the promise of gene therapy, but also the current realities and limitations (it should be emphasized, in particular, that some time will be required to develop the science of the field and to translate these advances to clinical practice).

SWITZERLAND

- *Federal Constitution of the Swiss Confederation*, (1999, September 2001 version), <http://www.swissemb.org/legal/const.pdf>
- *Federal Law of 25 December 2000 on Medicinal Products and Medical Devices (Law on therapeutic products) (Recueil officiel des lois fédérales)*, (November 2001), No. 47, pp. 2790-2833), http://www.swissmedic.ch/files/pdf/HMG_English_New_version.pdf
- *Ordinance of 17 October 2001 on clinical trials of therapeutic products (OClin)*, (Recueil officiel des lois fédérales, 28 December 2001, No. 51, pp. 3511-3524), http://www.swissmedic.ch/files/pdf/VKlin_e_2005-03-14.pdf (unofficial English translation)
- *Federal Act on Research on Surplus Embryos and Embryonic Stem Cells (Embryonic Research Act)*, (Approved by Referendum November 2004), <http://www.admin.ch/ch/f/ff/2003/7481.pdf> (in French)
Press release on the results of the referendum, http://www.admin.ch/cp/f/4200919c_1@fwsrv.g.html (in French)
- Swiss Academy of Medical Sciences, *Medical-Ethical Guidelines for Somatic Gene Therapy in Humans*, (1998), http://www.samw.ch/docs/Richtlinien/f_Somat_genth.pdf (in French)

Descriptive Synopsis

Legislative acts:

One of the main principles of the Swiss Constitution is the protection of human dignity and personality as well as a person's "genetic heritage." The ban on any manipulation of germ cells of human gametes and embryos in the constitution (Article 2(a)) is consistent with this principle. In addition, Article 119(1) states that human beings must be protected against any abuses connected with genetic engineering research.

The *Embryonic Research Act* provides protection against any abuse relating to embryonic research. In particular, Article 3 considers the modification of germ cells, the production of stem cells from any embryo whose germline has been modified, or the use of such cells to be "forbidden practices" sanctioned by penal clauses.

Concerning gene therapy specifically, the Swiss government enacted the *Law on therapeutic products 2000* and the *Ordinance on clinical trials of therapeutic products*

2001 to provide quality assurance and protection for patients who participate in gene therapy clinical trials.

The scope of the *Law on Therapeutic Products 2000* covers all clinical trials or therapeutic treatments, including gene therapy to the extent that the treatment directly relates to therapeutic products (Article 2). The law established the Swiss Agency for Therapeutic Products (Chapter 5) to authorize gene therapy protocols and ensure that all clinical trials are carried out in accordance with recognized principles of good clinical practice (Article 53).

In view of the provision pertaining specifically to clinical trials relating to therapeutic treatment in the *Law on Therapeutic Products 2000*, and in accordance with Article 2(1)c) of the law, the Swiss Federal Council enacted the *Ordinance on clinical trials of therapeutic products 2001*. The ordinance covers clinical trials of somatic gene therapy but excludes from its scope clinical trials that involve live human organs, tissues or cells, or “ex vivo gene therapy” (Article 2). The regulatory process for gene therapy is outlined in detail in the ordinance. Before commencing a clinical trial, the medical institute must obtain approval from the institutional ethics committee. The ethics committee must verify that the clinical trial respects ethical and quality standards. According to Article 4 of the ordinance, all clinical trials must conform to the Guidelines for Good Clinical Practice (GCP) adopted by the International Conference on Harmonization. For clinical trials of somatic gene therapy and of medicines containing genetically modified microorganisms, the ordinance requires authorization from the Swiss Agency for Therapeutic Products.

The agency evaluates the following:

- a. the risks relating to the therapeutic product tested;
- b. the risks relating to the clinical trial from the point of view of protecting humans and the environment, in particular concerning the possible dissemination of genetically modified organisms into the environment and their capacity to survive, to reproduce or to transfer genetic material; and,
- c. the security measures necessary for the protection of humans and the environment, in particular against any dissemination of genetically modified organisms into the environment during the clinical trial and during their transport, storage, and elimination (Article 16).

Before authorizing a clinical trial, the Swiss Agency must obtain a favorable decision from the Swiss Federal Office of Public Health, the Swiss Agency for the Environment, Forests and Landscape, and the Swiss Expert Committee for Biosafety (Article 17 of the ordinance).

Other normative measures:

The Swiss Academy of Medical Sciences (SAMS) published guidelines for somatic gene therapy in humans in 1998. The academy encourages somatic gene therapy but states that any modification of germline cells should be prohibited.

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Descriptive Synopsis

In 1989, the UK government established the Committee on Ethics of Gene Therapy, a non-statutory body, to provide ethical guidelines for research on the treatment of genetic disorders in adults and children through genetic modification of the cells of the human body (gene therapy). The committee published their report on gene therapy in 1992, which included definitions on somatic and germ line gene therapy and several recommendations regarding gene therapy in general.

The committee recommends that germline gene therapy be prohibited because of lack of knowledge regarding possible consequences, hazards, or harm to future generations caused by germline gene therapy.

According to the committee, somatic gene therapy is considered to be “making good a defective gene in the body cells where it is needed.” The aim of this category of gene therapy is to “provide the right genetic information, under proper control, in precisely those cells which need it for their normal function” and “to alleviate diseases in [an] individual and that individual alone.” The committee recommends that somatic gene therapy should be regarded as a discipline of research involving human subjects and that of the performance of gene therapy should be conditional upon satisfactory scientific, medical, and ethical review. The committee further recommends that a new supervisory body be set up and charged with the task of assessing and monitoring the scientific and medical complexities of gene therapy.

The UK government established the Gene Therapy Advisory Committee (GTAC) in 1993 to oversee and implement the recommendations.

Presently, the GTAC remains the only national research ethics committee for gene therapy clinical research. Its practices and procedures are set out in the *Medicines for Human Use (Clinical Trials) Regulations 2004*. All gene therapy clinical research, which involves somatic gene therapy or gene transfer research, must be approved by the GTAC. The GTAC does not consider any proposals for germline cell gene therapy, as it is considered unlawful. The GTAC states that, “the possibility of inadvertent targeting or modification of germ cells should be carefully assessed during pre-clinical studies. GTAC will need to be satisfied that measures are in place (requirement for the use of contraception) to protect against the patient conceiving a child during or shortly after the study.” (*Operational Procedures for the Gene Therapy Advisory Committee in its Role as the National Ethics Committee for Gene Therapy Clinical Trials 2004*).

The GTAC defines gene therapy as “the deliberate introduction of nucleic acids into human somatic cells for therapeutic, prophylactic or diagnostic purposes” (*Operational Procedures for the Gene Therapy Advisory Committee in its Role as the National Ethics Committee for Gene Therapy Clinical Trials 2004*). This definition incorporates all clinical trials that involve the use of techniques for delivering DNA or RNA into human subjects. In order to assess the research protocol, the GTAC are bound by the following principles:

- gene therapy is research and not innovative treatment;
- only somatic therapy will be considered; and,
- therapeutic research involving patients must not put them at disproportionate risk (for this reason gene therapy should be restricted to patients with serious disorders where current alternative treatments are not wholly effective).

The GTAC also requires that standard operating procedures be in place before the committee gives its approval for the trial to begin.

In 1998, the GTAC published its *Report on the Potential Use of Gene Therapy In Utero*. The GTAC concluded that:

- there were no new ethical issues raised by in utero gene therapy that were not already recognized in other interventions in utero, or in the use of gene therapy in other situations (the issue of consent remains a matter solely for the pregnant woman);
- in order to be ethical, the risks of the physical procedure would need to be known;
- the disorder or disease treated would need to be one that was life threatening or associated with severe disability, and for which no suitable treatment is available after birth, in order to justify intervention in utero;
- the use of direct or vector-mediated gene therapy in utero is unlikely to be acceptable in the foreseeable future, in view of the safety and ethical difficulties; and,
- such interventions could be considered by the GTAC in the same manner as somatic gene therapy, i.e. subject to the strict criteria already established by the committee.

Regarding tissue- and cell-based therapies, the UK has two main agencies that regulate therapeutic goods, devices and medicines. First is the Medical Devices Agency (MDA), which is the national agency responsible for regulating medical devices under the *Medical Device Regulations 2002*. The MDA published the *Code of Practice for the Production of Human-derived Therapeutic Products* in 2002 as a guidance manual for the production, quality assurance, and safety assessment of therapeutic products using human tissues or cells. The second agency is the Medicines Control Agency (MCA), a national agency responsible for the regulation of medicines under the *Medicines Act 1968*. In 2003 the two agencies were amalgamated as the Medicines and Healthcare Products Regulatory Agency (MHRA). Gene therapy products, whether devices or medicines, may fall under the regulatory authority of the MHRA.

Other normative measures:

In 2002 the House of Commons published the *Developments in Human Genetics and Embryology* report, which included a recommendation that the government conduct a thorough review of advice and regulations in the field of medical genetics, embryology, and reproductive medicine, with the purpose of establishing more streamlined structure in the field.

The Human Fertilization and Embryology Authority, in its *Code of Practice 2003*, explicitly prohibits “altering the genetic structure of any cell while it forms part of an embryo” (Section 10.4).

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Descriptive Synopsis

The United States has no federal legislation specifically addressing human genetic modification (either germline and somatic). However, the *Federal Food, Drug and Cosmetic Act* and the *Public Health Service Act* have been interpreted as providing sufficient authority for federal health agencies to regulate research on human genetic modification. Federal oversight for human genetic modification is characterized by the existence of numerous and often overlapping regulatory reviews required by local and federal agencies, such as the Food and Drug Administration (FDA) and the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH).

In addition to the abovementioned legislation, all institutions receiving federal funds must comply with federal rules regarding the protection of human subjects in medical research. These rules also apply to research conducted pursuant to an investigational new drug application (IND) or to support an application for a new drug or biological product. Following international standards, key aspects of the federal regulations are a review of research protocols by an Institutional Review Board, informed consent by research subjects, and periodic reporting.

Human germline genetic modification

Some authors have argued that the current ban on federal funding of embryo research seemingly prohibits conducting germline genetic modification interventions. Others argue that the Recombinant DNA Advisory Committee (RAC) would have to assert jurisdiction over such research protocols in order for some of this research to be precluded from receiving federal funding.

Under the 1996 Dickey-Wicker amendment it is illegal to use federal funds to support research “in which human embryos are created, destroyed, discarded, or knowingly be subjected to risk of injury or death greater than allowed for research on fetuses in utero under 45 CFR 46.204 and 46.207, and subsection 498(b) of the *Public Health Service Act*.” Moreover, the Dickey-Wicker amendment defines a human embryo as “any organism, not protected as a human subject under 45 CFR 46 as of the date of enactment of the governing appropriations act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.”

Likewise, state legislation banning or limiting embryo research may be applicable to the technologies of germline genetic modification.

Whereas the RAC of the National Institutes of Health has an explicit policy stating that it will not entertain requests or protocols for research involving human germline modification at this time, FDA has indicated that it will assert jurisdiction over proposals dealing with germline genetic modification in humans. FDA will require an investigational new drug application (IND) to be filed before the technology may be attempted in humans. Currently, there are no guidelines or regulations indicating the criteria FDA will use to evaluate such applications.

The NIH *Guidelines for Research Involving DNA Molecules* defines germline modification as “a specific attempt to introduce genetic changes into the germ (reproductive) cells of an individual, with the aim of changing the set of genes passed on to the individual’s offspring.”

Human Somatic Genetic Modification (“Gene Therapy”)

Governance of gene therapy research falls under the purview of NIH and FDA, both part of the Department of Health and Human Services.

The Secretary's Advisory Committee on Genetics, Health and Society is responsible for providing policy advice to the department on a broad array of complex medical, ethical, legal, and social issues raised by the development and use of genetic technologies. In turn, the Recombinant DNA and Gene Transfer section of the Office of Biotechnology monitors and approves scientific progress in basic and clinical research involving recombinant DNA and human gene transfer.

a) The National Institutes of Health (NIH)

While NIH's jurisdiction over gene therapy research is limited to those institutions and researchers that receive federal funding (either directly funded by NIH or conducted at or sponsored by NIH-funded institutions), their regulations are also voluntarily followed for privately funded research. NIH maintains a mandatory registry of all gene therapy protocols that receive federal funding. In the case of protocols funded entirely with private funds and not conducted at or by an institution receiving NIH funding, submission to the registry is voluntary.

The RAC, a public advisory committee to the director of NIH, has developed a set of federal guidelines that address the manipulation of genetic material through the use of recombinant DNA techniques (e.g. NIH Guidelines for Research Involving DNA Molecules). The RAC is in charge of examining clinical trials that involve the transfer of recombinant DNA and genes to humans, and focuses on the scientific, safety, and ethical issues that are involved. All human gene therapy trials funded by NIH, either directly or indirectly, must be approved and registered with the RAC.

RAC members include physicians, scientists, medical ethicists, consumer activists, and private citizens, as well as *ex officio* members of federal agencies, including FDA and the Department of Health and Human Services' new Office of Human Research Protection (OHRP).

FDA and NIH have complementary responsibilities with respect to the regulation of human gene therapy. FDA's primary job is to ensure the quality and safety of gene therapy products and that these products are properly studied in human subjects, while NIH's primary roles are to evaluate the quality of the science involved in human gene therapy research and to fund the laboratory scientists who invent and refine the tools used for gene transfer clinical studies.

b) Federal Food and Drug Agency (FDA):

FDA has asserted jurisdiction to regulate clinical applications of gene therapy based on the authority granted by the Federal Food, Drug and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHS Act).

According to FDA, "nucleic acids used for human gene therapy trials will be subject to the same requirements as other biological drugs." Consequently, FDA regards gene therapy as not fundamentally different from other types of therapies and thus as not requiring new oversight mechanisms.

In 1993 FDA issued a notice in the Federal Register further explaining the legal basis for its regulation of gene therapy. The notice defined gene therapy as “a medical intervention based on modification of the genetic material of living cells.” Such cells “may be modified *ex vivo* for subsequent administration or may be altered *in vivo* by gene therapy products given directly to the subject.” The genetic manipulation “may be intended to prevent, treat, cure, diagnose, or mitigate disease or injuries in humans.” According to the document, “[f]inal products containing the genetic material intended for gene therapy are regulated as biological products ... or as drugs ...”

As with germline genetic modification protocols, researchers conducting somatic gene therapy need to submit to FDA an IND application with preclinical data sufficient to justify use of the product in humans, and proof of approval from their Institutional Review Board (IRB).

The Center for Biologics Evaluation and Research (CBER) regulates human gene therapy products, which fall under the legal definition of a "biologic" product. CBER uses both the *Public Health Service Act* and the *Federal Food Drug and Cosmetic Act* as enabling statutes for oversight.

Biological products are approved for marketing under provisions of the PHS Act. However, because most biological products also meet the definition of "drugs" under the FD&C Act, they are also subject to regulation under FD&C Act provisions.