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Regulation of Gene Therapy in Europe: a Current Statement Including Reference to US Regulation

O. Cohen-Haguenauer

INTRODUCTION

OVER THE past decade, methods for delivering genes into mammalian cells, with the aim of subsequent expression of the transferred sequences from the host cell, have been developed. Potential therapeutic applications have been envisaged and have raised great interest.

It is generally accepted that no attempt to introduce germ line genetic alterations should be performed. This would result in introduction of genetic changes into the reproductive cells of an individual, with the aim of modifying genes passed on to the individual's offspring. This paper will only consider somatic cell gene therapy, where genetic modifications are applied to a single patient's somatic cells.

Although procedures based on specific gene targeting will not enter clinical protocols prior to solving fundamental issues, procedures based on addition of genetic material are currently underway. The expected benefit of genetic modification of somatic cells needs to be carefully assessed with respect to its potential risks. Whatever the technological strategy, non-propagation and non-transmission of the gene transfer delivery system is mandatory.

Preclinical studies covering a large range of pathologies are currently underway. These studies are primarily aimed at demonstrating the technological feasibility of various approaches rather than the true therapeutic efficacy. Technological improvements, and the solving of basic issues dealing with both the regulation of gene expression and the biology of cell transplantation, are still required in order that gene therapy may enter a clinical efficacy phase [1]. A multidisciplinary approach is needed to allow fruitful exchange between investigators in the basic sciences and clinical therapists. The European Working Group on Human Gene Transfer and Therapy (EWGT) was set up to meet this need.

Whatever the interest raised by gene therapy and its innovatory potential, the relevance of this approach should be carefully considered, both in terms of economical constraints and ethics, and in the context of an overall therapeutic strategy. This is particularly important in the case of acquired diseases, like cancer, and this new approach should be compared to alternative treatments, such as targeted drugs.

In principle, gene transfer involves the insertion of a foreign sequence of nucleic acid into the nucleus of a deficient target

Correspondence to O. Cohen-Haguenauer at the Laboratoire Transfert Génétique et Oncologie Moléculaire, Institut d'Hématologie, Hôpital Saint-Louis, 1, Avenue Claude Vellefaux, 75475 Paris Cedex 10, France. Dr Cohen-Haguenauer is the Scientific Secretary to the European Working Group on Human Gene Transfer and Therapy (EWGT) EWGT Central Office, Institut d'Hematologie, Hôpital Saint-Louis, 75475 Paris Cedex 10, France.
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cell. This transfer is mediated by a vector system carrying the nucleic acid sequence, which may be either virally-derived or macro-molecular. Recent data have also demonstrated efficient gene transfer through naked DNA sequences.

Current approaches to gene therapy use modified or attenuated viruses as vectors to carry the genetic material into the cell. Clinical protocols based on either defective retroviruses or defective adenoviruses are currently underway. Vector systems based on adeno-associated vectors and defective herpes viruses, with a natural tropism for the central nervous system, or rhinoviruses are being studied. Other gene therapy products that are under development use alternative delivery methods: DNA–liposome mixtures, directly administered naked DNA, and DNA combined with a targeted delivery system, such as a monoclonal antibody or cellular receptor targeted ligand conjugate. All these approaches must be regulated.

In the European Union, regulation will be controlled by the centralised licensing authority procedure within the forthcoming European Medicines Evaluation Agency. The Committee for Proprietary Medicinal Products (CPMP) has just released drafts (DGIII/5863/93 Draft 3, March 1994) [2] which are currently under review. In the U.S.A., the FDA is the relevant authority and a notice (Federal Register, October 14th, 1993) has been released dealing with applications to statutory authorities for human somatic cell therapy products and gene therapy products [3].

As the process of adding genetic material involves technology which may have side-effects, these, specific to both the disease and to each technological approach, should be taken into account.

A fundamental prerequisite is safety, whether concerning the patient or his environment. Whatever the technological strategy, non-propagation and non-transmission of the gene transfer delivery system is mandatory. The expected benefit of genetic modification of somatic cells should be carefully assessed and compared to the potential risk. The ethics of gene therapy is a major issue. In the U.S.A., the Recombinant DNA Advisory Committee (RAC) reviews clinical protocols. In addition to safety, the RAC releases recommendations following the scientific, clinical efficacy, social and ethical evaluation of each proposal. Intraction with the public is encouraged. There is no such federally established authority in Europe. Some member states have, however, developed *ad hoc* review processes which are further described in this paper.

I. DEFINITIONS

Gene therapy—somatic cell therapy

Gene therapy involves the deliberate modification of the genetic material of living cells. Cells may be modified *ex vivo* for subsequent administration, or may be altered *in vivo* by gene therapy products given directly to the subject. Genetic manipulation may be intended to prevent, treat, cure, diagnose or mitigate disease or injuries. When the genetic manipulation is performed *ex vivo* on cells which are subsequently administered to the patient, this is also a type of somatic cell therapy.

Somatic cell therapy involves the prevention, diagnosis and treatment of disease or injuries in humans by the administration of autologous, allogeneic or xenogeneic cells. These have been manipulated, altered or processed to change their biological characteristics *ex vivo*. Manufacture of products for somatic cell therapy involves the *ex vivo* propagation, expansion, selection, pharmacological or other alteration, of their biological characteristics.

Thus, administration of cells that have undergone *ex vivo* gene manipulation should be considered a combination of somatic cell therapy and gene therapy.

The safety and efficacy of any gene therapy procedure should be tested in clinical trials of appropriate design. This issue receives much public attention, which is of critical importance and benefit, but the manufacture and distribution of a product are also of importance.Regulation of these two areas is covered by different authorities: safety and efficacy by ethical committees and scientific review, and large scale production by medicine control agencies. In the European Union, gene therapy regulation is currently being investigated by medicine control agencies.

It should be mentioned here that strict adherence to the principles of good laboratory practice (GLP) [4–10] is mandatory, whether the concern is product quality, safety or efficacy in patients or in large scale production.

II. GENE THERAPY PRODUCTS

Quality, safety and efficacy aspects in the production of vectors and genetically-modified cells

As mentioned previously, a document has just been released by the CPMP [2] and is currently being discussed. The final version should be released by January 1995 and in the meantime, market authorisation will be submitted to Committee for Proprietary Medicinal Products Council regulation (EEC) 2309/93 [11].

The latter [1] states that "many of the principles laid down in existing Community guidelines on biotechnology products, such as requirements for cell banks, genetic stability and safety testing, would be applicable to the products designed for gene therapy".

Large scale production and safety aspects of biotechnology intended for the distribution of pure material with reproducible qualities (applied to biotechnology in general)

The manufacture of biological products is based on three fundamental principles:

1- Control of biological sources
2- Control of production processes
3- Control of the bulk and final product

It should be stressed that quality control for products as diverse as human blood derivatives and vaccines against viruses could, at least in part, be relevant for somatic cell and gene therapy. In general, it is more prudent to apply existing regulatory frameworks to products for gene therapy than to wait until the field has matured and new regulations determined [12–15].

The industrial viewpoint on safety aspects of biotechnology deals with the safety of both the product and the environment, as outlined below.

Product safety mainly deals with quality requirements which are uniform from one country to another, and addresses the pharmaceutical criteria required for biotechnological drugs. Regulatory bodies put great emphasis on a strict adherence to good manufacturing practice (GMP) [16].

Safety for the environment is concerned with the setting up of biotechnology facilities with efficacious containment policies adapted to the biohazard level of the microorganism. This is aimed at protecting the product, the worker and the environment.

The development of recombinant DNA technology has induced public fear and speculation regarding potential risks,

and has resulted in considerable variations in the regulatory guidelines related to the environment. Some countries have over-regulated, thereby reducing competitiveness, particularly in Europe. However, standardisation is in process through the implementation of EC Biotechnology Directives.

Requirements for large-scale fermentation processes using recombinant microorganisms will be reviewed on the basis of regulations or guidelines originated from both EU and the U.S.A.

II-A.1.0 Safety aspects related to the product

Safety aspects related to the product mainly address quality, which is a prerequisite for administration in humans.

Principles governing the quality of biotechnology products derive from those governing biologics in general. These processes involve living organisms, and thus variability is of major concern. Regulatory bodies put great emphasis on adherence to GMP standards which are mainly based on manufacture in adequate facilities, stringent in-process controls, final product testing, extensive validation programs.

1.1 *Regulatory framework.* Although general regulations for biologics and drugs apply to products produced by recombinant DNA technology, specific regulations have been established both in the EU and the U.S.A. to provide guidance for production and quality control.

In the EU, a dedicated working party was created in 1985 by the European Commission [12–15]. This working party has established guidelines in consultation with industry:

—Guidelines for the production and quality control of medicinal products derived by rDNA technologies (1987) [17], monoclonal antibodies of murine origin (1987) [18], monoclonal antibodies of human origin (1990) [19], cytokines (1990) [20].

—Guidelines for the validation of virus removal and inactivation procedures (1991) [21].

—Guidelines for minimising the risk of transmission of agents causing spongiform encephalopathies via medicinal products (1991) [22].

—Biotech headings for notice to applicants (1992) [23].

In the U.S.A., several "points to consider" (PTC) documents have been issued by the FDA:

—Points to consider in the production and testing for new drugs and biologicals produced by recombinant DNA technology (1985) [24].

—Points to consider in the characterisation of cell lines used to produce biologicals (1987) [25] and (1993) [26].

—Collection, processing and testing of *ex-vivo* activated mononuclear leucocytes for administration to humans 1989 [27].

—Human somatic cell therapy and gene therapy (1991) [28].

—Supplement to [24]: nucleic acid characterisation and genetic stability (1992) [29].

These "guidelines" and "points to consider" are not intended to be definitive or comprehensive and will be reviewed with new developments.

Although these requirements are uniform from one country to another, divergent decisions have been taken by various authorities. In order to avoid this, regulation guidelines were selected as a topic for discussion at the 1993 International Conference on Harmonization (ICH).

It is important to note that GMPs are applicable during the entire production process, starting with the constitution of the cell banks and proceeding through final packaging, labelling and distribution. The existing GMP regulations addressing the manufacture of biologicals issued by the EEC [16] and the U.S.A. [30] are considered to be broad enough in scope to be applicable to all biologics.

1.2 *Biotechnology facility requirements.* The first condition for manufacturers to meet GMP requirements is to have adequately equipped facilities [16].

—Living organisms must be handled in conditions where their living potential during storage and culture is maintained.

—Most biologicals and components are good substrates for microbial growth. Microbial contamination must be considered at every step of the process from the cell banks to aseptic filling of final containers.

—Biologicals are often heat labile and some steps (particularly purification) must be performed under controlled conditions.

—A clear separation between contained and non-contained areas should be settled.

—During production of a product, no other process should be handled simultaneously in the same area or by the same persons in an adjacent area.

1.3 *In-process control.* The requirements in all countries stress the need to base quality not only on the identity and purity of the finished product, but also on in-process control. As these processes deal with living organisms, it is essential to demonstrate the ability to reproduce results at each step of the process.

Establishment of a cell bank system is mandatory and consists of the following: (1) master cell bank (MCB) where aliquots of vials originated from a single primary culture are conserved. (2) working cell bank (WCB) or manufacturer working cell bank (MWCB). From one vial of the MCB, the WCB is prepared through the same process. The banks are stored in conditions which give assurance of genetic stability. Large scale production is initiated from one vial, and a new WCB is prepared when the previous one has been depleted.

Genetic stability must be maintained during storage, also during production and post-production phases.

Analysis of initial batches should be undertaken to establish reference values with regard to identity, purity and potency. Thereafter, a more limited series of tests may be appropriate.

1.4 *Validation.* Validation is a critical aspect of quality control and must be undertaken at different levels:

—Validation of equipment and services

—Validation of analytical methods

—Validation of the production process.

All these should specifically meet criteria defined in EU guidelines for viral validation [21].

II-A.2.0-Safety aspects related to the environment

Some countries, such as Germany and Denmark, have over-regulated this area. After several years of experience, an Organization for Economic Cooperation and Development (OECD) working group published general guidelines in 1986 [31], developing in particular the concept of Good Industrial Large Scale Practice (GILSP). A second report was recently published [32] which updates and further develops safety considerations.

In order to harmonise regulations, three directives were adopted by the Council:

—Containment of genetically modified organisms (GMOs) to protect workers and the environment during the production process. This is governed by application at the national level of the EC Directive (90/219/EC, DG XI) on the contained use of

genetically modified microorganisms [33] and covers; genetic modification of somatic cells as well as culture, storage and use in laboratory or hospital facilities of genetically modified somatic cells; preparation in contained facilities of genetically modified viruses; treatment of patients with genetically modified viruses in contained facilities, provided that the patient will not shed infectious particles.

—The potential adverse consequences of the deliberate release of GMOs (e.g. recombinant viruses) into the environment. This is also governed nationally by the application of the EC Directive (90/220/EC, DG XI) on the deliberate release of genetically modified organisms [34] where products, such as recombinant viruses in the form of aerosol spray, are used for the treatment of genetic diseases.

From January 1995, the deliberate release of medicinal products consisting of or containing GMOs will fall within the scope of Council Regulation (EEC) 2309/93, which provides for a specific environmental risk assessment similar to that laid down in Directive 90/220/EEC.

—Directive 90/679/EC on the protection of workers protects workers from risks related to exposure to biological agents while at work [35].

Members states of the then European Community were to have implemented the provisions of these directives as national laws by October 1991. Difficulties have been encountered, however, and implementation is still in process. The situation can be summarised as follows:

Some countries have met many of the requirements, though the precise mechanisms differ (U.K., Germany, The Netherlands, Denmark, France). Others have neither drafted national legislation nor established any regulatory or advisory committees.

A consensus is proving elusive, although the directives are sufficiently flexible enough for each national authority to interpret them in a manner which reflects the existing national procedure, and will not prevent some countries from overregulating.

The official bodies, designated by individual member states, that will issue licenses, enforce measures and form the inspectorate differ in nature and mission: the Ministry of Health (Italy), lander authorities (Germany), the Ministry of Environment (Denmark). Divergent decisions are a possible outcome.

II-B. Regulation specifically applying to gene therapy products

Gene therapy products are produced in three steps, each of which should be regulated:

(1) Cloning, isolation and amplification of the therapeutic nucleic acids sequences. Amplification is usually achieved in a microorganism, i.e. bacterial host or eCR.
(2) Introduction of the therapeutic sequences into a vector system which may consist of mere plasmid DNA, or rather defective viral vector system or synthetic macromolecular complexes.
(3) Transduction of the target cells mediated by the vector system.

The therapeutic benefit, if it exists, should be achieved as a result of a combination of all three. In addition to regulations applying to each independent step, specific attention should be given to the end-point product, which might result in additional levels of concern for functional or pathological consequences including the unexpected.

II-B.1.0 Compromising factors

Certain factors may compromise the consistency, safety and efficacy of gene therapy products and should be given special attention:

1.1 *Homogeneity.* Since the "therapeutic" nucleic acid sequence requires amplification, uncertainties over the fidelity of the replication systems raise concerns about the homogeneity of the amplified product. Evidence that the correct sequence has been made and has remained stable during the amplification steps, before and following transfer, should be demonstrated. A detailed description of the cloned gene should be given, including details of its origin, identification and isolation as well as its nucleotide sequence. Any intended modifications to the gene, compared with its natural counterpart, should be detailed.

1.2 *Complexed nucleic acid as vector.* A complete description of the manufacturing procedures used in vector production should be provided, together with a complete description and characterisation of all the materials used to form these vectors. Where appropriate, materials should be of pharmaceutical quality. Some products may be manufactured as components of the final vector, which is constituted just prior to use (e.g. expression constructs complexed with polymers). In these cases, all components of the final gene transfer vector should be characterised.

1.3 *Virus vectors raise particular issues regarding manufacture and safety.* Viruses proposed as vectors could produce pathological effects under certain circumstances. Viral vectors should lack viral genes (encoding structural and enzymatic proteins) that are required for replication and viral particle formation. Sequences known to be associated with pathological effects should be deleted. Full documentation on the origin, history and other characteristics of the parent virus, current virus stocks and methods of propagation should be provided, and a full description of the viral constructs is mandatory. A full sequence of the construct should be provided whenever possible, or a complete restriction map of the construct.

Replication-deficient viruses are propagated in special "packaging" cell lines modified to express the viral proteins necessary for the recombinant genomes to be replicated and packaged. The aim should be the construction of packaging cell lines which make the production of replication-competent (infectious) viruses, by recombination with the viral genome of the gene transfer vector used, impossible. One method to do this (e.g. for retroviruses) is to separate the genes encoding the viral structural and enzymatic proteins, and to express them from separate constructs which are inserted into separate chromosomal integration sites. To further minimise the risk of recombination within the packaging cell line, packaging cell lines containing any endogenous viral sequences that could complement the recombinant viral genome should be avoided. Precautions must also be taken to prevent infection of the packaging cell line by wild-type viruses that might lead to the formation of replication-competent recombinant viruses.

It should be stressed that the so-called "ping-pong" procedure should be strictly avoided in the generation of producer clones, as the resulting increase in virus titres might originate from generation of replication-competent particles with high frequency.

Routine batch control analysis should include evaluation of identity, purity and efficacy/potency. For estimating the efficacy/potency of vectors, biological tests should be applied that permit

the efficiency of gene transfer and the level and stability of therapeutic gene expression to be determined. Wherever possible, a reference batch of vector of assigned potency should be established and used to calibrate tests. Suitable ways for expressing the potency of vectors should be established and results reported.

Quality control of the manufactured product (i.e. cell bank characterisation) should involve both the testing of viral supernatant and co-culture onto appropriate permissive cell lines to exclude the presence of replication-competent virus. With large scale production, transduced target cells in which additional helper viruses may arise, must also be tested. Where replication-competent viruses are detected, the whole batch should be rejected.

1.4. *Genetically modified somatic cells might constitute products.* For example, a therapeutic gene may be transferred to, and expressed in, fibroblasts, myoblasts, epithelial cells or other cell types, and these expanded *in vitro* to sufficient numbers for inoculation into one or more patients having the same condition. Alternatively, the genetically modified cells may be grown in collagen-lattices or other appropriate matrices to produce neoorgans that secrete a particular therapeutic protein. Full documentation of the origin; history, construction and characteristics of the genetically-modified somatic cells should be provided. The homogeneity and genetic stability of the cells should be demonstrated or thoroughly investigated. A well-defined master and working cell bank should be established, where appropriate.

1.5. *Direct* in vivo *gene transfer.* In this case, special attention should be given to the risk for genetic modification of germline cells.

1.6 *Vectors.* The most frequently used vectors in current clinical protocols for somatic gene therapy are derived from murine retroviruses. Safety considerations are relatively well defined, particularly at the level of viral producer cell lines [36–38].

Types of potential biological problems with retrovirus vectors [38] are as follows:

(1) Intrinsic: integration to the host genome. Possible biological problems with retrovirus vectors relate to the process of random integration into the host genome. Integration in transcriptionally active regions may take place in essential cellular genes, or insertional activation of a proto-oncogene (not sufficient to induce malignancy unless cell-specificity of insertion) could occur. Additionally a tumour suppressor gene may be disrupted.

Such risks exist, albeit at a lower level than the random integration of any foreign DNA sequence. The affected cells may, however, acquire tumorigenic potential. Oncogenesis is generally regarded as a multi-step process involving dysfunction of several genes, the single-site insertional mutagenesis may only carry a very low risk. The risk is obviously increased in a construct randomly integrating high copy numbers per cell.

(2) Formation of replication-competent retrovirus could, in theory, arise from either homologous recombination with endogenous viruses known in mouse genomes, non-homologous recombination with endogenous viral sequences in the human genome or even pseudotyping of naturally occurring viral genomics. There may also be a low risk that the recombinant viral genome itself recombines with the genomes of co-infecting viruses, which could be originated from a contaminating virus in medium, helper cells or inocula to produce novel recombinant viruses. This may lead to non-target cells being transduced (e.g. germline cells being transduced with vector nucleic acid) and a risk of its horizontal spread to clinical staff and members of the public.

New recombinant viruses might be generated, the consequences of which are unpredictable.

Whether murine viruses have pathological potential in humans is not clear; but lymphomas have been reported in monkeys following the use of amphotropic retroviral supernatants contaminated by helper virus [39].

II-B.2.0. Clinical assessment

Long-term patient follow-up will be essential. Ideally patients should be monitored for:

—Survival of genetically-modified somatic cells.

—Biodistribution or anatomical location of the genetically-modified somatic cells.

—Quantification of the therapeutic product engineered by genetically-modified somatic cells.

—Toxicity and potential adverse effects including the development of antibodies to the therapeutic protein, the genetically modified somatic cells, the vector or those cell antigens modified as a consequence of the presence of genetically modified somatic cells and/or vectors (especially where repeated administration is intended).

—Viral vector shedding whenever viral vectors are used, as this may result in infections spreading to clinical personnel, relatives and other close contacts (see Directive 90/220/EEC).

II-B.3.0. Regulation of human somatic cell therapy products and gene therapy products by the FDA in the U.S.A.

The FDA mainly deals with manufacturing facilities and the licensing of products. A document was released in October 1993 [3] which intended to clarify the regulatory approach and provide guidance to manufacturers of products intended to be used in somatic cell therapy or gene therapy.

The FDA focuses on the development of safe and effective biological products from first use in humans to commercial distribution [3, 40]. FDA premarket approval is required for all biological products.

In general, somatic cell therapy and gene therapy products based on viral vectors meet the statutory definition of biological products and are thus subject to appropriate regulation. Nevertheless, some products should be regulated as drugs, e.g. gene therapy products such as chemically synthesised compounds meet the definition for a drug but not for a biological product.

Some products may even contain a combination of biological compounds and drugs or devices. Under a provision of the Safe Medical Devices Act of 1990, the FDA determines the primary mode of action of the combination products, then assigns the primary juridiction for review.

Technical requirements are less stringent during the early phases of clinical investigation. The status of the product is that of an investigational drug (IND). Clinical trials are therefore to be conducted under INDs. IND application should include descriptions of the following:

—Molecular biology of vector and insert.

—Production and testing of the producer cell banks.

—Safety testing of the final viral supernatant.

—Safety and activity testing in the animal.

—Specifications and required testing at each step of the production process.

The Intended population, together with the expected risk/benefit, should be defined (see below: RAC).

Later developments require a product license which involves licence of both product (Product License Application, PLAs) and manufacturing facilities (Establishment License Application, ELAs).

Biological products intended for use as source materials for further manufacture into licensed somatic cell therapy products or gene therapy products require premarketing approval, as do biological products intended for further manufacture when they are shipped from one legal entity to another.

II-B.4.0. *Appropriate assays for the detection of replication competent viruses (schematic frame)*

4.1. *Levels of testings: recommended testing for RCR.*

—Cell bank characterisation

MCB:

Supernatant testing + amplification on permissive cell lines

Coculture + permissive cell lines

MWCB:

Confirmation of negative RCR by one of the tests used in MCB

Post-harvest testing

—Transduced target cells

—Patient follow-up

4.2. *Retroviruses as vectors for gene transfer* [41].

—Cell bank characterisation

(1) Leukaemia negative S + L-assay: feline PG-4 cells: focus forming units (ffu) on a lawn of PG-4 cells.

(2) 3T3 amplification assay (one or two weeks) allows for amplification of a small number or even a single RCR. This is useful in detecting RCR which might theoretically arise following multiple recombinational events occurring within the producer cells.

(3) Additional lines—
Human diploid fibroblast IMR-90.
—Mus dunni cells: permissive to multiple RCR types
→wider range than S + L−.

(4) Co-cultivation
—3 weeks post-harvest: self co-culture period.
—2 weeks on Mus dunni cells; then S + L- test on the super.

(5) Helper rescue assays/mobilisation = the most sensitive tests—3T3BAG.
—*dunni* G1Na.

(6) PCR; RT assays: far less sensitive.

—In patients (according to recent recommendations released by FDA)

(1) In patients treated with supernatant for the first 3 months, sample serum monthly for

—reverse transcriptase assay

—PCR on to envelope sequences

—PCR for RCR, then quarterly, then every year.

(2) Following intracerebral implantation of producers

In addition to above mentioned tests:

—Tests for RCR in peripheral blood lymphocytes

—Test for the presence of antibodies against mouse cells

4.3 *Adenoviruses as vectors.*

—RCR

—PCR for E1A

—Biological assay (PFUs) lysis

—AAV biological testing

—Acquired immunity.

III. CLINICAL TRIALS—ETHICAL AND SCIENTIFIC REVIEW PROCESSES

Gene therapy raises questions that are scientific, ethical and social. They arise at the level of the single patient, at the level of the carer and at the level of the environment in general.

At the level of the individual patient, the ethical issues surrounding gene therapy are no different from those related to other new therapeutic approaches. Potential benefits must be shown to outweigh potential risks. The rationale for any gene therapy proposal must, therefore, take into account the possibility of any alternative treatment strategies. There may, in some instances, be no alternative to gene therapy.

Public health considerations relate in particular to the possible spread of helper virus either to carers, to families or to the general population and environment.

The safety and efficacy of gene therapy procedures should be tested in clinical trials of appropriate design. Regulation of safety and efficacy is subject to ethical committees and scientific review, and is covered by different bodies according to the country where the trials are performed.

The review process is the most comprehensive in the U.S.A. A large number of protocols have already been reviewed over several years, some of which have been rejected or secondarily withdrawn.

III-A. The U.S.A.

The RAC of the National Institutes of Health (NIH) deals with ethical and social concerns, scientific evaluation and public discussion.

A document has been released which is intended to provide guidance in preparing proposals for NIH consideration under section III-A-4 of the NIH Guidelines for Research Involving Recombinant DNA Molecules [42]. Experiments involving the transfer of recombinant DNA into human subjects require review by the NIH, RAC and approval by the NIH. RAC consideration of each proposal is on a case-by-case basis and follows publication of a précis of the proposal in the Federal Register, an opportunity for public comment and a review of the proposal by the RAC. Recommendations on each proposal are forwarded to the NIH Director for a decision, which is then published in the Federal Register.

The "Points to Consider in the Design and Submission of Human Somatic Cell Gene Therapy Protocols" was originally adopted by the RAC in 1986. This initial document has been revised under the title of "Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA into the Genome of Human Subjects" [42].

These "Points to Consider" apply to research conducted at, or sponsored by, an institution that receives any support for recombinant DNA research from the NIH. Other researchers are also encouraged to use the "Points to Consider".

Following a general introduction, the document is divided into four parts:

Part I requests a description of the protocol with special attention to the short-term risks and benefits of the proposed research both to the patient, and to others; patient selection criteria, informed consent; privacy and confidentiality.

In Part II, investigators are requested to address special issues pertaining to the free flow of information about the clinical trial.

Part III summarises other requested documentation that will assist the RAC in its review of proposals.
Part IV specifies reporting requirements (at 6-month intervals with any serious adverse effects reported immediately).

The RAC overseas investigational gene therapy protocols (federal funded or performed in institutions receiving federal funding), and offers an opportunity for broad public discussion, thus dealing with social/ethical concerns together with scientific evaluation.

A trial proposal will be considered by the RAC only after the protocol has been approved by the local institutional biosafety committee (IBC) and by the local institutional review board (IRB) in accordance with Department of Health and Human Services (DHHS) "Regulations for the Protection of Human Subjects". The IRB and the IBC may, at their discretion, condition their approval on further specific deliberation by the RAC.

III-B. In Europe

There are no comparable European Union (EU) authorities for gene therapy. Although individual countries such as France and the U.K. have national regulatory agencies in place, others like Germany only require local and state approval. The ratification of a German "gene law" is currently underway. In Italy, the Minister of Health is currently preparing notes for guidance. Details are given concerning currently available regulation in both the U.K. and France.

U.K.

1.1 *The gene therapy advisory committee.* In 1989, Health Ministers sanctioned the Committee on the Ethics of Gene Therapy (CEGT). The CEGT reported its findings in 1992. In accordance with CEGT recommendations, the Government established the Gene Therapy Advisory Committee (GTAC), to replace CEGT, in November 1993. The CEGT reviewed the first UK proposals for gene therapy. The Committee's terms of reference are to consider and advise on the acceptability of proposals for gene therapy research on human subjects on ethical grounds, taking account the scientific merit and potential benefits and risks of the protocol; to work with other agencies in the field, including local research ethics committees and agencies with statutory responsibilities such as the Medicine Control Agency, the Health and Safety Executive and the Department of the Environment; to provide advice to Health Ministers on developments in gene therapy research and their implications.

As with RAC in the U.S.A., a case-by-case review and approval by GTAC must be obtained before gene therapy or gene transfer research is conducted on human subjects. One of the Committee's first priorities has been the production of guidance for those submitting gene therapy protocols. These guidelines are near completion and will provide a U.K. equivalent of the NIH/RAC "Points to Consider" guidance.

1.2 *Local research ethics committee.* Any research involving NHS patients, including their records, or which uses NHS premises must be referred to, and gain the approval of, a local research ethics committee (LREC). This is applicable also to gene therapy trials. The final judgement of the GTAC is transmitted to LRECs as well as to the proposers.

1.3 *Medicines control agency (MCA) (U.K. licensing authority).* The MCA considers product licence applications and clinial trial certificates under the provision of the Medicines Act 1969. Before testing in patients, investigators must apply for a certificate of exemption. An interim document from the U.K., MCA is currently available entitled "Guidance notes on applications to the Medicines Control Agency for clinical trials of gene therapy (18.8.93)".

France

1.1. *National advisory committee on ethics (CCNE).* This independent body was created in 1982. It is not intended to legislate, its role is purely advisory. The Committee is a reference point for the National Assembly, the Senate, a member of the government, a public institution, a foundation or any individual or association. It may also make the decision on the necessity of releasing comments on specific subjects. A positive statement was made in December 1990 regarding use of somatic gene therapy, whereas deliberate modification of germ-line cell genomes is strictly forbidden. Gene transfer into human embryos is also prohibited due to the risk for subsequent germ-line cells modification. These statements were not followed by the release of a Points to Consider type document.

1.2 *The commission de genie genetique (CGG) and the commission de genie biomoleculaire (CGBM).* These two Commissions are in charge of regulation dealing with national implementation pertinent to EEC Directives on "Controlled use of Genetically Modified Microorganisms". CGG is connected to Ministries of University Education and Research and also the Environment; CGBM has connections with the latter and the Ministry of Agriculture.

1.3. *Local research ethics committee: Comité Consultatif de Protection des Personnes se prêtant à des Recherches Biologiques (CCPPRB).* The CCPPRB deals with the protection of human beings who participate in biomedical research and any trials must be approved by a research ethics committee (CCPPRB).

1.4 *Medicines control agency (Agence du Médicament): commission of viral safety.* This Commission is connected to the French Ministry of Health and deals with viral validation. More recently, a working group has been established within the MCA to provide guidance for achievement of marketing authorisation of gene therapy products.

A common centralised single file including appended documents, each dedicated to a specific commission, should be released soon, in order to simplify the submission process involving at present four separate Commissions.

1.5. *Parliament.* The French law on bioethics is currently being discussed in the parliament, modifications are scheduled for every 5 years.

Harmonisation in Europe is anticipated through regulation processes mediated by MCAs and by centralised procedures for licensing authorisation within the forthcoming European Medicines Evaluation Agency.

It is not yet clear whether additional specific regulations dealing with social, ethical and scientific issues will be established at the level of the EU, although the field might benefit from formalisation of currently available recommendations and from the consultation of experts at the European level for the design and review of clinical protocols. The EWGT is willing to help serve these goals.

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News

18th Annual Physicians Cancer Symposium, U.S.A.

This symposium, sponsored by Scripps Memorial Hospital, Stevens Cancer Centre, U.S.A., will be held at Sheraton Harbour Island, San Diego, U.S.A. on 6–8 October 1994. For more information, please contact the Cancer Symposium, 2603 Main Street, Suite 690, Irvine, California 92714, U.S.A. Tel. 800 321 6338; Fax 714 752 7444.

4th Nottingham International Breast Cancer Conference

This conference is to be in Nottingham, U.K. on 20–22 September 1995. For more information, please contact Mrs Wendy Bartlam, Conference Secretary, Professorial Unit of Surgery, City Hospital, Nottingham NG5 1PB, U.K. Tel. 0602 625707; Fax 0602 627765.

4th International Congress on Oral Cancer

This conference will be held in Ogaki City, Japan on 20–23 September 1995. It will be multidisciplinary, bringing together surgeons, radiotherapists, chemotherapists, epidemiologists, researchers, pathologists and paramedical personnel from various disciplines for scientific deliberations on upper aerodigestive cancers. For more information, contact the Secretariat, 4th International Congress on Oral Cancer, Department of Oral and Maxillofacial Surgery, Asahi University School of Dentistry, 1851-1, Hizumi, Motosu-gun, Gifu 501-02, Japan. Tel. 81 5832 6 6131 ext. 1472; Fax 81 5832 7 4364.