

Title : Euregenethy-Newsletter : Regulation of Gene Therapy in Europe-a scientific network of users

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EUREGENETHY

Regulation of Gene Therapy in Europe

a scientific network of users

<http://193.48.40.240/www/euregenethy/euregenethy.html>

A concerted scientific input in Regulation of Gene Therapy = the spirit of Euregenethy

Gene Therapy : prospects and limitations

Potential applications of gene therapy are extremely large extending from monogenic hereditary disorders to acquired and multifactorial disorders. Therapeutic gene transfer addressing such a large panel of conditions is currently being investigated. Gene therapy holds great promises in applications where experimental research demonstrates significant progress and is expected to translate into clinical efficacy for instance : cardio-vascular diseases, where restenosis and atherosclerosis can be improved; cancer with attempts at inhibiting tumour growth *via* antiangiogenesis interventions or use of modified dendritic cells as a way to achieve immunotherapy; transplantation of bone-marrow or solid organs transplantation including xenografts; long-term expression of transgenes in hematopoietic progenitors; inborn errors of metabolism where *in vivo* modification of hepatocytes would operate; neurologic disorders with implantation of immuno-excluded growth-factors secreting cells or use of both viral and non-viral vectors, as new pathways bringing up therapeutic options in diseases where none had been available to date. Hence, great uncertainty still surrounds the technical, clinical and commercial developments of gene therapy as important issues in each of these areas remain unsolved. At the scientific level, fundamental technical problems need to be overcome, namely, improvements in the efficiency, targeting and safety of gene delivery systems.

Why is there a need for regulation of gene therapy?

This area of biomedicine involves novel therapeutic interventions by means of genetic modification (including stable with a theoretical risk of insertional mutagenesis) of living cells eventually using new biologicals as vectors. Among these, defective viruses do harbour risks for generation of replication competent helper virus and further spread.

The development of recombinant DNA technology has induced in the public fears and speculation regarding its potential risks. In fact, implementation of gene therapy involves technological approaches which might not be devoid of potential side effects (as with many conventional therapeutic means addressing severe conditions). There are different levels where quality and safety need to be ascertained : the patient, the carers and the environment. Safety and regulatory aspects of gene therapy can be envisaged along three lines :

- 1 st/ experimental and preclinical research;
- 2nd/ manufacture of gene therapy products;

3rd/ clinical trials and development. There are elements within existing regulations that apply to the development of gene therapy approaches. Additional regulation of gene therapy will be needed as this field adapts to evolving knowledge. More specific to gene therapy is the level of complexity resulting from the various critical levels of concerns : gene discovery; gene regulation; gene delivery systems with potential biohazards; manufacture of biotechnology products and finally, efficacy and safety outcome following treatment of a patient.

The regulation of Gene Therapy is intended to assess for these risks in order to restrict them; and also delineate a margin where safety is most likely secured.

Regulation of gene therapy: current status

Worldwide harmonisation of regulation based on scientific knowledge is needed in order to foster development of international exchanges. Current status in various countries demonstrates a high level of heterogeneity. To date the implementation of Gene Therapy clinical trials in Europe is being regulated at two distinct levels, without overlap:

SUMMARY

A concerted scientific input in Regulation of Gene Therapy = the spirit of Euregenethy 1

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1. Early phases of clinical trials are currently being reviewed at the national level; the process is not harmonised from one country to the next;
2. Marketing authorisation is being covered by the centralized procedure through the European Medicines Evaluation Agency (EMA), entering into force on 01.07.95, and involving a decision binding on all Member States of the European Union (Regulation [EEC] Nr. 2309/93). The CPMP (Committee for Proprietary Medicinal Products) has adopted guidance to support marketing authorization of gene therapy products (December 1994: III/5863/93 Final); these guidelines are currently being revised. It is expected that Guidelines integrating quality, safety and arranged along scientific and pragmatic rationale will be available europewide and homogeneously implemented. Towards this end sustained interaction is required between the scientific community and regulatory authorities, in particular the EMA and the CPMP, as well as with regulators in charge with the review of clinical trials in their early phases, at the national level.

Interaction is required between all regulatory authorities and scientists/ users: EUREGENETHY workprogramme/ A DGXII Biomed2-ELSA-Concerted Action

From the standpoint of "Gene Therapy Users" working in close collaboration europewide, homogeneity and coherence are required in order to exchange technologies and assess for efficacy. Current heterogeneity justifies to conduct a survey/ record and translation (into a europeanwide understandable language) of national regulations; as well as to circulate expert information related to european regulation to potential users. This represents the basis for the Euregenethy workprogramme. Such an input should ultimately contribute to harmonisation *via* dissemination of knowledge and expertise. Multidisciplinarity only allows for fruitful exchanges between investigators in the basic sciences, therapists, the pharmaceutical industry and officers in charge with regulation of gene therapy.

The Euregenethy network involves the contribution of expert users from 15 european countries. A series of tasks have been undertaken along a science-based rationale and from a user's standpoint. These include :

1. making a record of regulatory information from each member state; a summary of regulation in each country is currently available on the web; it represents the content of this first letter of information;
2. English translation and circulation of key national reference documents;

3. circulation of information including both national and overall regulation by means of telematics [Euregenethy home page address : <http://193.48.40.240/www/euregenethy/euregenethy.html> and support of Europe-based journals, specialising in this field;

4. a record of regulatory information from the EU;

5. survey of the opinions of the European Group of Ethics and of the Unesco International Bioethics Committee;

6. fostering interaction between all interested parties, and in particular scientists and physicians with regulators. A first multidisciplinary forum will take place in June 99 gathering for the first time national officers in charge with regulation in each member state and at the centralised level (EMA), delegates from the European Commission III and XII, together with FDA and RAC, OECD, industrial platforms, involving EU-Biotech companies, the European Society on Gene Therapy (ESGT), patients' and GCP panels. Our purpose is to provide users with relevant information and ultimately contribute to harmonisation.

The wide range of applications of Gene Therapy actually cross calls out a majority of Biomedicine research areas. Cooperation between Academia and Biotech companies is compulsory in order to establish favourable conditions for the development of gene therapy. Meanwhile, this sector is likely to provide strong opportunities for Hitech employment.

Odile Cohen-Haguenaer, Coordinator
(see back page for list of partners and contacts)

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Pr Heinz Zwierzina 01/1999

Introduction

Work with genetically modified organisms and the application of gene analysis and gene therapy are regulated by the Austrian Gene Technology Law (GTG). The Austrian Federal Chancellery is the relevant authority, decision-making is supported by the Commission for Gene Technology (Gentechnikkommission).

Intervention of the germline is generally prohibited by the Austrian Gene Technology Law (§64).

Preclinical research

Work with genetically modified organisms (GMOs) as well as their release must be conducted according to the Austrian Gene Technology Law (GTG) (see also Council Directive 90/220/EEC).

Every institution intending to perform gene analysis must announce the project and its purpose by filling out a form pursuant to the GTG (§65 to §72) and sending it to the Austrian Federal Chancellery. The institution where gene analysis will be performed, the name and qualifications of the head of the laboratory and working staff and the existence, number and arrangement of rooms and equipment used must be declared. Precautions concerning data protection must be in place.

A project leader with sufficient practical experience in working with GMOs must be defined and must guarantee that safety regulations will be complied with. A committee for biological safety must be established for each institution working with gene technical methods. The applicant must define the safety level and the planned biological safety measures. Safety measures must comply with the state of the art in science and technology in order to minimize the risks entailed with GMOs. Experiments must be performed in laboratories of one of the four safety levels (S1-S4) having the necessary equipment.

In case of uncertainty the institution in charge (Austrian Federal Chancellery) will decide based on a hearing of the referring committee for biological safety and representatives of the Commission for Gene Technology.

Any release of a GMO must be publicly announced. The deadline for filing a written objection is three weeks.

If animals are to be involved in the experiment, the regulations must comply with the Austrian Protection Law ("Tierschutzgesetz").

Manufacture

GMP (Good Manufacturing Practice) must be implemented as defined by the GMP guidelines of the EC and WHO.

The Federal Chancellery and the Ministry of Social Affairs are the responsible corporate bodies. Manufacturing authorization is required for manufacturers who intend to commercially or professionally distribute the drug to others.

Clinical Trials

Gene therapy comprises DNA, viral or non-viral vectors and genetically modified somatic cells.

Somatic gene therapy may only be performed by a physician working at an approved hospital and permission must be requested by the medical director of the institution. The study coordinator for a clinical trial must document his experience in performing phase I trials.

Every institution intending to perform gene therapy or analysis must announce the project and its purpose by filling out a form pursuant to the Austrian Gene Technology Law (§74 to §79) and sending it to the Austrian Federal Chancellery. Precautions concerning data protection must be in place, and the existence and purpose of medical consultations as well as the qualifications of the consulting medical doctor must be declared.

The final decision is made by the Federal Chancellery based on a hearing together with the Commission for Gene Technology.

Detailed information can be received from the Federal Chancellery: "Informationsblatt zu Antragsunterlagen für klinische Prüfung zum Zweck der somatischen Gentherapie".

Positive appraisal by a local, independent ethics committee formed according to the law of the state where the trial is performed is required before initiation of a clinical trial. If the trial is performed in various institutions, all relevant ethics committees must give their appraisal.

Marketing authorization

Marketing authorization for gene therapy is subject to the centralised EC regulation by the EMEA.

Contacts for further information

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Belgium

Myriam Sneyers - 03/1999

Definition and General Comments

In Belgium, there is no legal definition of gene therapy nor are there specific regulations.

Nevertheless, the involvement of genetic manipulation at any step of the development chain of a gene therapy medicinal product automatically implies the application of the biosafety regulation *i.e.* the EC Directives 90/219 and 90/220 which regulate the uses of genetically-modified organisms in the European Union. Indeed, Belgian regulation integrates research, development, clinical research and manufacturing towards gene therapy in the general frame of biosafety regulation. Moreover, the biosafety regulation in Belgium copes with all known gene therapy approaches: viral-derived vectors as well as cell-mediated somatic gene therapies as the non viral-vectors and naked DNA issues and the allo- or xenografting/transplantation using transgenic material.

To secure administrative and scientific coordination between the different Belgian authorities concerned by biosafety, a Cooperation Agreement was established [reference 1] installing a common scientific evaluation system between the Federal State and the Regions concerning biosafety. This advisory system consists of a consultative Biosafety Council and a Service of Biosafety and Biotechnology (SBB) which also acts as secretariat of the Council. The Biosafety Council or the SBB assesses the safety of activities using GMO's and pathogens. The Council must be consulted in the case of deliberate release activities and also in the case of some contained use activities (*e.g.*: new programs of gene therapy clinical trials). The Council consists of representatives of the Regional Governments and Federal Ministries of Public Health and Environment, Agriculture, Science Management and Work Protection. The Council is assisted by experts; an *ad hoc* expert group "Recombinant viral vectors, virosomes, recombinant vaccines, gene therapy" has been constituted.

The Service of Biosafety and Biotechnology has adopted the following definition of human gene therapy: "transfer of genetic material in human bodies for therapeutic or diagnostic purposes".

As far as germ-line gene therapy is concerned, the SBB refers to the opinion of the Group of Advisers on the Ethical Implications of Biotechnology (GAEIB) to the European Commission which stated that "... germ-line therapy on humans is not at the present time ethically acceptable..." [reference 2].

To obtain more information about biosafety in Belgium, the Belgian Biosafety Server (<http://biosafety.ihe.be>) can be consulted.

Preclinical research

As far as biosafety is concerned, research and development and animal experiments related to gene therapy are covered within the scope of the Directive 90/219/EEC. The three Belgian Regions have implemented this Directive in the frame of their environmental legislations for classified installations. Even if there is a specific regulation for each region [references 3-5] and different competent authorities, the scientific purposes and advisory bodies (Biosafety Council and Service of Biosafety and Biotechnology) are the same for the three regions. These regulations do not only apply to the contained use of GMOs defined in the Directive 90/219/EEC but also to the use of GMOs as well as human, animal and phytopathogens.

To obtain an authorization from the regional competent authority to carry out a gene therapy activity or program in a given installation and having the required environmental permit, the notifier must fulfill the so-called REC2 form (information required from the Directive 90/219/EEC) and submit it to the Service of Biosafety and Biotechnology. The applicant must document the goals and methods used for the planned activities, the duration, the genetically modified organism(s) involved, the risk and the containment level including work practices adopted as a result of the risk assessment of biological tools.

Experimental work in gene therapy that needs authorization includes the construction, use, storage and inactivation of vectors for gene therapy. Experiments involving the use of GMOs and/or pathogens have to be performed in laboratories and/or animal facilities at one of the four biosafety levels. These facilities can be visited by the advisory body and/or the competent authority for authorization delivering as well as by inspection bodies. The delay to obtain the authorization is maximum 60 days.

In addition, other important regulations may also apply :

- the regulation on the protection of workers exposed to biological agents [reference 6];
- the regulation over the protection of animals used for experiments [reference 7];
- the regional regulations on medical wastes (references 8-10).

Manufacture

Regulations on the contained use of GMOs must also be applied to manufacturing facilities of gene therapy products.

Manufacturing authorization for gene therapy products or any other medicinal product is granted by the Ministry of Public Health [reference 11]. This authority is also responsible for inspections. In the case of manufacturing of a new medicinal product to be used for therapeutical trials, derogations can be obtained.

GMP (Good Manufacturing Practice) must be implemented as defined by the GMP guidelines of the EC [reference 12].

GLP (Good Laboratory Practice) is required in some cases according to the Belgian regulation on this subject [reference 13] and as defined by OECD recommendations.

Clinical trial

A clinical trial can only be conducted if it satisfies several independent regulatory requirements which are described below.

- In Belgium, all clinical trials must be submitted to local "Committees of medical ethics" which depend on the "National Council of the Order of Medical Doctors" and which must be created in order to obtain the hospital agreement [reference 14]. Ethical and medical aspects of gene therapy clinical trials in particular, clinical relevance, potential therapeutic efficiency and content of the document "informed consent of the patient", are covered by these agreed "Committees of medical ethics". If the trial is performed in various institutions, all relevant ethics committees must give their approval.

Until now, the Belgian advisory committee of bioethics [reference 15] has never been consulted for gene therapy related issues.

- Good clinical practices have to be applied [reference 16].
- Each clinical trial must be notified to the General Inspection of Pharmacy [references 11, 16] but there is no review process nor written authorization.
- As far as biosafety regulations are concerned, clinical research in gene therapy using transgenic material and/or pathogen organisms must be submitted to the contained use procedure according to the Belgian regulations which implement the Directive 90/219/EEC (see preclinical research).

The following authorization procedure has to be followed: after an informative meeting with the SBB, the applicant (the investigator) can introduce his dossier to the SBB; the dossier is reviewed by the advisory body which transmits its advice to the competent regional authority for final decision; in case the hospital where the trial takes place has already an environmental permit, the decision is delivered after maximum 60 days, otherwise it takes 90 days. The clock is stopped when additional information is needed. The dossier is constituted by the so-called REC2 form with its annexes and with its public counterpart (annex to form PUB), by the protocol(s), the GMP file, the approval of the local Committee of medical ethics and also by the specific questionnaire for gene therapy clinical trials. This specific questionnaire derives from the NIH guidelines for research involving DNA molecules (Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects). All parts of the dossier can be written in Dutch, in French or in English except the form Annex PUB which must be written in the official language of the region where the trial will take place.

The major outlines taken into consideration from the biosafety point of

view for the review of the dossier are: the aim(s) of the gene therapy tool and the clinical trial; the type of clinical trial (multiphasic or not, multi-country or not, pilot trial or clinical development program); the structure and properties of the biological system used, including quality aspects; the *in vitro* and *in vivo* pre-clinical data and risk assessment studies including the description of gene transfer system(s) and the expression of therapeutic inserts and associated physiology issues; the environmental risk assessment including a monitoring program for patient follow-up; the qualification of the staff and the adequacy of the laboratory and clinical facilities and management. Only the biosafety aspects, defined as the safety issues for the human health and for the environment, are reviewed by the advisory body; the balance benefit/risk is not taken into consideration.

The dossier is reviewed by the Biosafety Council or by the SBB itself. The choice between the Biosafety Council and its *ad hoc* experts group or the SBB depends on the degree of familiarity of the Biosafety Council with the proposed gene therapy tool. If a dossier concerns a gene therapy tool already evaluated by the Biosafety Council or substantially equivalent to it, the SBB can refer to the previous advice of the Biosafety Council and analyse itself the specificities of the submitted dossier.

In case of authorization, the activities which imply gene therapy clinical trials must respect the regional regulation on contained use as well as the specific conditions established by the scientific evaluation system on a case by case and mentioned in the official authorization. These conditions are essentially related to the containment criteria, the biosafety monitoring of the patient, and to the report content that the responsible for the activity might provide to the Biosafety Council.

The authorization can not only be given for a particular protocol, but for a whole program of clinical trials in a given installation for several years (usually 5 years). This program may cover several protocols of the same kind (*e.g.* phase II and III protocols using one type of vector with one gene of interest in a determined therapeutic area, etc.) which can be considered equal with regard to biosafety aspects. Also, after clinical research has been approved in a given installation with reference to the first submitted protocol, changes (*e.g.* a new protocol, new formulation of or new specifications for the gene therapy product) can be allowed thereafter with small delays if there is no modification in the biosafety frame of the program. The Belgian regulatory system thus appears to be very flexible.

The Biosafety dossier is the official reference document as well for the Biosafety Council and its experts as for the public and the authorities. The advice of the Biosafety Council and the non confidential part of the biosafety dossier are transparent and can be submitted to public hearing.

In the case of multicentric trials and/or ambulatory medicine with a risk of excretion of GMOs by the patients, the Belgian regulation [reference 17] which implements the Directive 90/220/EEC on the deliberate release of GMOs can/must also be applied. The application is submitted to the General Inspection of Pharmacy which thereafter transmits the dossier to the Biosafety Council. The dossier contains the same information as the dossier for a contained use activity except that it must not contain the REC2 form but rather the Summary Notification Information Format (SNIF) referred to in Article 12 of Council Directive 90/220/EEC [reference 18]. The SNIF needs to be completed in English and also in the language(s) of the region(s) involved by the trial. The review process of the dossier is similar to the contained use one. The two procedures can be managed together. The maximum delay to deliver the authorization is 90 days.

Marketing authorization

In the European Union, since 1995, the centralized procedure for marketing authorization through the European Medicines Evaluation Agency (EMA), involving a decision binding on all Member States of the European Union (Council Regulation No [EEC] 2309/93) has to be applied. The CPMP (Committee for Proprietary Medicinal Products) has adopted guidance to support marketing authorization of gene therapy products (December 1994: III/5863/93 Final); these guidelines are currently being revised.

Moreover, in the case of Medicinal products containing or consisting of GMOs, the Council regulation No (EEC) 2309/93 provides for a specific environmental risk assessment equivalent to that laid down in Annexes II and III to Directive 90/220/EEC. In case Belgium is reporter of such a dossier to the CPMP the Belgian general inspection of pharmacy (Ministry of Public Health) must submit the dossier to the Biosafety Council for advice [reference 18].



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2. GAEIB's Opinion N° 4 of 13 December 1994.
3. Besluit van de Brusselse Hoofdstedelijke Regering van 9 december 1993 betreffende de inrichtingen die activiteiten verrichten waarbij pathogene of genetisch gemodificeerde micro-organismen of organismen worden aangevend/ Arrêté du Gouvernement de la Région de Bruxelles-Capitale du 9 décembre 1993 relatif aux installations effectuant des opérations mettant en œuvre des micro-organismes ou des organismes, pathogènes ou génétiquement modifiés.
4. Besluit van de Vlaamse regering van 1 juni 1995 houdende algemene en sectorale bepalingen inzake Milieuhygiëne (Hoofdstuk 5.51. Biotechnologie)/ Arrêté du Gouvernement flamand du 1^{er} juin 1995 relatif à la Biotechnologie (chapitre 5.51. du VLAREM II).
5. Arrêté du Gouvernement wallon du 13 juin 1996 modifiant le Règlement général pour la protection du travail en ce qui concerne l'utilisation d'organismes génétiquement modifiés et/ou pathogènes/ Besluit van de Waalse regering van 13 juni 1996 tot wijziging van het Algemeen Reglement voor de arbeidsbescherming, wat het gebruik van genetisch gemodificeerde en/of pathogene organismen betreft.
6. Koninklijk besluit van 4 augustus 1996 betreffende de bescherming van de werknemers tegen de risico's bij blootstelling aan biologische agentia op het werk/ Arrêté royal du 4 août 1996 concernant la protection des travailleurs contre les risques liés à l'exposition à des agents biologiques au travail.
7. Koninklijk besluit van 14 november 1993 betreffende de bescherming van proefdieren/ Arrêté royal du 14 novembre 1993 relatif à la protection des animaux d'expérience.
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9. Arrêté du Gouvernement wallon du 30 juin 1994 relatif aux déchets d'activités hospitalières et de soins de santé/ Besluit van de Waalse Regering van 30 juni 1994 betreffende de afval van ziekenhuis- en gezondheidszorgactiviteiten.
10. Besluit van de Vlaamse regering van 17 december 1997 tot vaststelling van het Vlaams reglement inzake afvalvoorkoming en -beheer (VLAREA)/ Arrêté du Gouvernement flamand du 17 décembre 1997 fixant le règlement flamand relatif à la prévention et à la gestion des déchets.
11. Koninklijk besluit van 6 juni 1960 betreffende de fabricage en distributie in het groot en de terhandstelling van geneesmiddelen/ Arrêté royal du 6 juin 1960 relatif à la fabrication et à la distribution en gros des médicaments et à leur dispensation.
12. Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use and the guide to good manufacturing practice for medicinal products.
13. Koninklijk besluit van 27 oktober 1988 betreffende de toepassing van de beginselen van goede laboratoriumpraktijken en het toezicht op de uitvoering ervan bij proeven op scheikundige stoffen/ Arrêté royal du 27 octobre 1988 relatif à l'application des principes de bonnes pratiques de laboratoire et à la vérification de sa mise en application pour les essais effectués sur les substances chimiques.
14. Koninklijk besluit van 12 augustus 1994 tot wijziging van het koninklijk besluit van 23 oktober 1964 tot bepaling van de normen die door de ziekenhuizen en hun diensten moeten worden nageleefd/ Arrêté royal du 12 août 1994 modifiant l'arrêté royal du 23 octobre 1964 fixant les normes auxquelles les hôpitaux et leurs services doivent répondre.
15. Samenwerkingsakkoord houdende oprichting van een Raadgevend Comité voor Bio-ethiek, gesloten te Brussel, op 15 januari 1993 tussen de Staat, de Vlaamse Gemeenschap, de Franse Gemeenschap, de Duitstalige Gemeenschap en de Gemeenschappelijke Gemeenschapscommissie goedgekeurd door een wet van 6 maart 1995 voor de federale overheid, door decreet van door decreet voor elk van de drie bovenvermelde Gemeenschappen, respectievelijk op 6 december 1993, 16 maart 1994 en 15 juni 1994 evenals door ordonnantie van 20 maart 1995 voor de Gemeenschappelijke communautaire Commissie/ Accord de coopération portant création d'un Comité consultatif de bioéthique, conclu à Bruxelles, le 15 janvier 1993 entre l'Etat, la Communauté flamande, la Communauté française, la Communauté germanophone et la Commission communautaire commune, approuvé par une Loi du 6 mars 1995 pour l'Autorité fédérale, par décret en date respective des 6 décembre 1993, 16 mars 1994 et 15 juin 1994 pour les trois Communautés susdites ainsi que par ordonnance du 30 mars 1995 pour la Commission communautaire commune.
16. CPMP/ICH/135/95 Step 5 Note for Guidance on Good Clinical Practice (CPMP adopted July 96).
17. Koninklijk besluit van 18 december 1998 tot reglementering van de doelbewuste introductie in het leefmilieu evenals van het in de handel brengen van genetisch gemodificeerde organismen of producten die er bevatten/ Arrêté Royal du 18 décembre 1998 réglementant la dissémination volontaire dans l'environnement ainsi que la mise sur le marché d'organismes génétiquement modifiés ou de produits en contenant.
18. Commission decision 92/146/EEC of 11 February 1992, concerning the Summary Notification Information Format referred to in Article 12 of Council Directive 90/220/EEC.



Denmark

Peter Hokland – 1999



Definition and General Comments

No central agency exists in Denmark dealing specifically with issues regarding products employed to transfer genetic material, which can be used in diagnostic and/or therapeutic intent. Rather, it was decided following a public and parliamentary debate in 1996 that, existing legislation was flexible enough to encompass these issues as well.

Thus, the Danish Medicines Act (Lægemiddeloven; 5101-10-1993 of July 1995) and the Danish Act on Scientific Ethical Committee System and the Handling of Biomedical Research Projects (Act no. 503 of June 24 1992) accommodate all aspects of gene therapy. These documents are in compliance with extensive number of EEC directives on the management of production and clinical trials on gene technology, first and foremost the directive dated April 23, 1990 on contained use of genetically modified organisms (90/219/EEC), but also the directive on the deliberate release of genetically modified organisms (90/220/EEC).



Preclinical Research

Applications have to be submitted to the Danish Medicines Agency for control of the quality of the product to be administered (*i.e.* patient safety), while the Danish Working Environment Service will subsequently have to approve the facilities in term of health personnel protection. The following documents have to be followed:

1. *Contained use.* The Danish Medicinal Products Act (5101-10-1993 of July 1995). This act is in full compliance with the EEC Directive 91/356 of June 13, 1991.

2. *Deliberate release.* The act mentioned above also applies here.

3. *Protection of workers.* This area is dealt with by the Danish Working Environment Service (Proclamation 864 of November 10, 1993), which is pursuant to the guidelines in EEC 90/679. This process requires prior submission of a standardized application.

Manufacture

GMP has to be followed as stipulated by international guidelines. Following approval of the protocol, an essential feature of the Danish system is the approval of the set-up, *i.e.* shipment and all aspects of local handling of genetically modified organisms. This involves a review of all procedures by the Danish Working Environment Service. This will have to take place for each site, where parts of the given GT protocol is to be instituted, and it involves a detailed standardised 15-points description of the process.

Clinical trial

The science and rationale is evaluated by the Danish Medicines Agency, which also in different sub-departments looks at the data on experimental efficacy and pharmaco-toxicology.

The ethical issues are covered by the Ethical Committee Systems, which is performed county-wise with a central unit (the Danish Control Scientific Ethical Committee) governed by the Act on this issue (Act no 503 of June 1992). While every protocol is to be submitted to the local committee, it must be envisaged that in a foreseeable future, all protocols on GT will automatically be re-routed to the central unit in order to secure uniform treatment.

Subsequently, the Danish Data Protection Agency is required to approve the establishment of the database containing all patient data. Application is individual, but a one-page form containing core information is also to be submitted.

Monitoring of side-effects is done by the principal investigator and is open to review by the Danish Medicines Agency. A centralized database containing such data is located within the framework of the Danish Medicines Agency.

Marketing authorization

The Danish Medicines Agency (under the Danish Board of Health) will review the application and documents related to it including validation and quality control measures.

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Odile Cohen-Haguenauer - 12/1998 - updated 04/1999

Definition and General Comments

Gene therapy products are defined as any product used to transfer genetic material which can be used for therapeutic, diagnostic and prophylactic purposes. Only somatic gene therapy is considered acceptable as ruled on by the French National Ethics Committee (CCNE).

Regulation of Gene Therapy has been placed under a specific Law (May 28th, 1996). This Law introduces a novel type of therapeutics namely, biological products of therapeutic benefit. GT products can follow either of two regulatory statuses: "proprietary medicinal product" or not. The latter statuses take into account differences in: - the type of product, - the scale of manufacture, - the nature of the disease and the private or institutional affiliation of sponsors/developers. The implementation of gene therapy-clinical trials is placed under the regulatory control of the "Agence française de sécurité sanitaire des produits de santé" (AFSSAPS ; "French Agency on sanitary safety of health products" now substituting the french medicines agency, Agence du Médicament). A single file being submitted to the Agency (as opposed to five different bodies until 1996). A "high Council of Gene and Somatic Cell Therapies" reports to the Prime Ministry on orientations intended to favour developments and coordinate the action of Institutions and private organisations involved.

Before initiating a GT clinical trial in France, at least four bodies have to give their approval, each of them serving a separate and necessary purpose. Final authorization is granted by the AFSSAPS's head. A specific streamlined procedure has been set up. GT trial sponsors have to submit a single dossier to the AFSSAPS according to a specific application format. This thirty pages document represents a comprehensive approach of safety and efficacy issues relating to Gene Therapy clinical trial in human:

1. information on the GMOs/ Containment and risk for deliberate release ;
2. pharmaceutical and biological information (strategy, gene construct and gene delivery system, manufacture and control, intended product-use *ex vivo* or *in vivo*, storage and destruction ;
3. pharmaco-toxicology relating to : the gene, the delivery system, the therapeutic product as a whole ;
4. clinical trial (rationale, goals, patients, treatment, evaluation and assessment criteriae, implementation procedure, patient follow-up);
5. declaration of severe adverse events.

Preclinical research

Two commissions are in charge with regulation of GMOs. These are the results of implementation of EEC Directives on "Controlled use of Genetically Modified Microorganisms" at the national level.

•The "Commission de Génie Génétique" (CGG) is responsible for the implementation of EC-Directive 90/219 in order to establish the relevant level of containment. CGG is connected to both the Ministry of University-Education and Research and the Ministry of Environment

•The "Commission de génie biomoléculaire" in charge with implementation of EC-Directive 90/220 connected to the Ministry of Agriculture and Ministry of Environment.

Manufacture

The legal status of gene transfer and gene therapy products is defined in 1996-Law. It is much alike medicines yet not registered as pharmaceutical drugs. Firms-plants and institutional centers involved in the preparation/conservation/ distribution/ importation and shipment require specific accreditation.

Review of manufacturing processes, quality of end-product (clinical grade) and inspections are placed under the AFSSAPS ("French Agency on sanitary safety of health products"). GMP and GLP apply to this section (ref : CPMP/ ICH).



Clinical trial

The review process currently involves the following:

- The AFSSAPS (“Agence française de sécurité sanitaire des produits de santé”, in English: “French Agency on sanitary safety of health products”) reviews the dossier for the quality, safety and clinical aspects. The AFSSAPS forwards it to the CGG and CGB for simultaneous evaluation of GMOs-related issues. As soon as the evaluation by the CGG, CGB and Agence is complete, the Agence’s director can authorise the start of the clinical trial. It is stated in the legislation that the review process should not exceed three months with the following exception: in case major additional questions are forwarded to the sponsor, the clock is stopped until answers are being received.
- As genetically modified organisms, gene therapy products are submitted to July 13th, 1992 Law implementing EC-Directives and statutory order of November 6th, 1995, putting deliberate release of GMOs intended for human use under the responsibility of the AFSSAPS. The latter decides whether or not expertise is required from the CGB.
- Local bioethics committees (CCPPRB for “Comité Consultatif de Protection des Personnes se prêtant à des Recherches Biologiques”). The terms of reference of which are also defined under 1988-Law (Huriet). Any research involving patients, including their records, must be referred to and gain the approval of a local research ethics committee.
- The dossiers are drafted and their evaluation conducted according to CPMP/ICH/135/35 guideline on Good Clinical Practice (GCP).



Marketing authorization

In the European Union, this level of regulation is to be covered by the centralized procedure for marketing authorization through the European Medicines Evaluation Agency (EMEA), entering into force on 01.07.95, and involving a decision binding on all Member States of the European Union (Regulation [EEC] Nr. 2309/93). The CPMP (Committee for Proprietary Medicinal Products) has adopted guidance to support marketing authorization of gene therapy products (December 1994: III/5863/93 Final); these guidelines are currently being revised. From January 1995, the deliberate release of Medicinal products containing or consisting of GMOs for the purpose of placing them on the market 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.



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References

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2. Cell and gene therapies : loi n° 96-452 du 28 mai 1996
3. Clinical trials and ethics : loi Huriet n° 88-1138 du 20 décembre 1988, modifiée par la loi n° 90-459 du 2 juillet 1990, la loi du 28 mai 1996 (Art. 219-18-2) et par la loi n°98-535 du 1er juillet 1998, visant à protéger les personnes se prêtant à des recherches biomédicales
4. Health safety : loi n°98-535 du 1er juillet 1998.
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Germany

Dr Klaus Cichutek - Dr Felicia Rosenthal
12/1998, revised 05/1999



Introduction

Definition: Gene therapy and somatic cell therapy products used *in vivo* are medicinal products according to the German Drug Law (AMG; “Arzneimittelgesetz”). They include DNA, viral or non-viral vectors and genetically modified autologous, allogeneic or xenogeneic cells (used *in vivo*) and are often summarised under the term “gene therapy drugs” in Germany. No official definition of the term “gene therapy drug” is given in the AMG. Regulation is provided by the AMG and the professional law of physicians. Application of GMOs and therefore of gene therapy drugs in humans is not regulated by the German Gene Technology Law (GenTG). Approval of deliberate release according to the GenTG is not required. Regulations are identical for gene therapy drugs and other drugs.



Preclinical Research

Experimental work in gene therapy including the construction, use, storage and inactivation of vectors, genetically modified bacterial or mammalian cells or animals has to be conducted according to the German Law on Gene Technology (GenTG; “Gentechnikgesetz”; transformation of Council Directives 90/219/EEC and 90/220/EEC).

Experiments involving the use of genetically modified organisms (GMOs) have to be performed in laboratories or animal facilities of one of four safety levels (S1 to S4), which are accordingly equipped.

Laboratory approval is given by the competent authority of the Land (“Bundesland”) for the GenTG. Experiments in safety level 1 laboratories only have to be documented and the competent authority has to be notified, whereas experiments falling under higher safety levels need additional approval by the same authority (3 months or less).

The Central Commission for Biological Safety (ZKBS; “Zentrale Kommission für die Biologische Sicherheit”, secretariat located at the Robert-Koch-Institut, Berlin) provides a list containing the safety level classifications of “standard” vectors or plasmids and GMOs and is in some cases (e.g. approval of safety level 3 operations) to be consulted by the competent authority of the Land for the GenTG.

Other laws and regulations that may apply (which are executed by different competent authorities of the Land where the laboratory is located):

- the law on epidemics (“Bundesseuchengesetz”, to be replaced by the “Infektionsschutzgesetz”);
- the law on animal protection (“Tierschutzgesetz”);
- the law on human embryo protection (“Embryonenschutzgesetz”);
- the radiation protection ordinance (“Strahlenschutzverordnung”);
- the ordinance on the use of hazardous substances (“Gefahrstoffverordnung”).



Manufacture

• GMP (Good Manufacturing Practice) has to be implemented as defined in the “Operation Ordinance for Pharmaceutical Entrepreneurs (PharmBetrV; “Betriebsverordnung für pharmazeutische Unternehmer”); see also: GMP guidelines by the WHO, EC and PIC.

• GLP (Good Laboratory Practice) is required in certain cases according to the German law on the use of chemical substances (ChemG; “Chemikaliengesetz”).

• Manufacturing authorisation is necessary for manufacturers who intend to commercially or professionally distribute the drug (and the active ingredient) to others. It is granted by the authority of the Land, where the facility is located, competent for the AMG (§ 13 AMG). This authority is also responsible for inspections and supervision (§ 64 AMG).

• Notification of the competent authority of the Land for the AMG is necessary beforehand for companies and establishments (also clinical

departments) which develop, manufacture, test, package drugs or subject them to clinical trials (§ 67 AMG).

Clinical Trial ("Klinische Prüfung")

In the guidelines "Richtlinien zum Gentransfer in menschliche Koerperzellen", published by the German Medical Association the requirement to use gene therapy drugs during clinical trials only is stressed. Clinical trials can only be conducted, if certain requirements are met (see §§ 40, 41 AMG).

- **Positive appraisal** of a local, independent ethics committee formed according to the law of the Land, where the trial is performed, is required before initiation of a clinical trial (see § 40 (1) AMG for exception). If the trial is performed in different clinics, all relevant ethics committees have to give their appraisal. No IND approval by a higher federal authority is necessary.

- **Notification** of the competent authority of the Land for the AMG and deposition of the clinical study plan is required. This authority is also responsible for inspections and supervision of the trial.

- **Submission** of documents (presentation according to § 40 AMG; forms available by Internet: <http://www.dimdi.de/germ/amg/klifo.html>) including the positive appraisal of the local ethics committee(s) and the pharmacological-toxicological data (see German Directive "Arzneimittelprüfrichtlinien" for content) to the competent federal higher authority for the AMG. The competent authority is either the Paul-Ehrlich-Institut, Langen, for gene therapy drugs which are vaccines or blood preparations or the Federal Institute for Drugs and Medical Devices (BfArM), Berlin, for other gene therapy drugs (see § 77 AMG). The trial can only be initiated after written confirmation of the competent higher authority that all documents required have been received.

- **Positive appraisal** (written form or hearing) is given by the Commission for Somatic Gene Therapy of the German Medical Association (KSG-BAEK, "Kommission für somatische Genterapie der Bundesärztekammer", required according to the professional law of physicians; see "Richtlinien zum Gentransfer in menschliche Koerperzellen", Deutsches Aerzteblatt 92, Heft 11, B-583-B588 [1995]).

- Registration of the clinical trial and patients involved with the German Gene Therapy Register (DGTR, "Deutsches Genterapie-Register") at the German Working Group for Gene Therapy (DAG-GT) and the publication of the protocol is recommended.

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Greece

Dr Dimitri Loukopoulos - 1999



Definition and General Comments

The introduction and use of "medicinal products" in Greece is controlled by various laws and regulations which are adapted to those of the European Union. The competent Authority for whatever is related to the approval and use of medicinal products is the "National Drug Organization" (EOF) which is a semi-autonomous body depending from the Ministry of Health. To process the ever increasing number of applications for new medicinal products in compliance with the regulations of the European Union, EOF uses a staff of several pharmacists and other scientists (internal and external assessors/experts) and proceeds to the release of the drug in the market after obtaining advice from several scientific Committees formed by prominent members of the medical community and other scientists (staff and advisors). When matters of general policy occur, the Ministry may form its own *ad hoc* Committees (usually attached to the Central Council of Health) which give advice to the Minister of Health.

For the time being, there are no specific requirements related to gene therapy in Greece. However, in case an application towards gene therapy were submitted, the EOF should follow the EU Guideline 75/318 EEC "Gene Therapy products : quality aspects in preparation of vectors and gene therapy in somatic cells". To better harmonize the various procedures, representatives of EOF have occasionally participated in various European Union Committees on this matter but have not yet come up with precise national rules. On the other hand, the Ministry of Health has recently formed an official Committee to deal with this pressing question with the mandate :

- to assist in the development of basic and preclinical research in the field of gene therapy;
- to define the safety requirements which must be met by the proposed systems of gene therapy, prior to their application in humans;
- to define the context which will allow the application of gene therapy in accordance with the international rules of scientific research and bioethics;
- to act as advisory body to the KESY (The Central Council on Health) with regards to the acceptance or rejection of the clinical trials which may be proposed,
- and to define the prerequisites which appear to be mandatory for the safety of the medical and paramedical staff and the relatives of the patients, when the latter receive gene therapy with potentially transmissible systems.



Preclinical research

Information to be completed



Manufacture

Not appropriate



Clinical trial

The interested scientist obtains permission to carry out the trial on his patients by the Administrative Committee of his hospital. To this effect he must submit: (a) the approval of the Scientific Committee of the Hospital, (b) the des-

cription of the medication with the expected effects and potential side effects, (c) the attestation that all patients entering the study are duly insured by the Company producing the drug and (d) a guarantee that all expenses associated with the trial will be covered by the Company or the scientists involved (please, don't ask for orphan medicinal products). As yet, Greek hospitals do not have "Ethics Committees" in the proper sense, *i.e.*, committees comprising, in addition to the medical members, scientists of other disciplines, although this measure is foreseen in various regulations and will eventually be implemented. For the time being, this role is taken up by the Scientific Committees. Be this as it may, after the agreement of the Hospital is obtained, then the application goes to EOF for the second stage, *i.e.* the formal and final licence of the trial, which implies (a) some kind of monitoring by the respective division of EOF, (b) free release of the medication through the customs and other administrative steps. The main prerequisite for licencing a clinical trial is that the drug will be provided free of charge.



Marketing authorization

On completing these steps and forming a satisfactory and adequate dossier, the company may apply formally to EOF for licencing the medication. Medicinal products (or modifications of medicinal products) which undergo the procedures of the EU usually pass these steps by "mutual recognition" or by "centralized procedures". Biotech and High technology products normally go through the latter procedure within the context of EMEA.



Contacts for further information

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Italy

Dr Cecilia Melani - Dr Giorgio Parmiani
06/1998, revised 02/1999



Definition and general comments

"Somatic Gene Therapy" (GT) defines medical interventions aimed at the deliberate modification of somatic cell genetic material for prevention, diagnosis or treatment of pathologic situations. Only somatic gene therapy is considered acceptable and any intervention aimed at modifying the germline is prohibited.

Genetic modification can be obtained by *in vitro* manipulation or directly *in vivo* by administration of vectors able to transfer functional genes and therefore modify the genetic inheritance of target somatic cells.

GT products include free or complexed nucleic acids, viral vectors and genetically modified cells. Most gene therapy products are classified as "Genetically Modified Organisms" or GMOs, whose confined use and deliberate release are regulated by two Legislative Decrees (n° 91/93 and n° 92/93). Moreover, the Legislative Decree n° 626/94 (implementing EC Directive 93/38/EEC) on the protection of workers exposed to biological

agents, applies to the manipulation of GMOs.

Different National Bodies are responsible for controlling and approval of the different phases of GT studies, namely experimental research, preclinical testing and clinical trials. The National Committee on Biosafety and Biotechnology (appointed by the President of the Ministries Council) establishes risk group of biological agents, evaluates guidelines for safety procedures and verifies the compatibility with already existing regulation. The National Committee on Bioethics (appointed by the President of the Ministries Council) is an advisory committee generating opinions on bioethics applying also to GT. The National Institute of Health-ISS works as National Review Board for GT. It provides opinions in order to set up experiences with new drug not previously used in humans. The Ministry of Health (Department of Prevention and Department of Medicine Evaluation) is responsible of the authorizations for the different phases of GT studies.

From a regulatory point of view, the existing legislative provisions appear to cover adequately the different aspects of pre-clinical studies, handling and production of GT products on a small scale, although procedures dealing with authorization and control of GT clinical trials await a more specific definition. Moreover, due to the lack of connection with industry, researchers often face regulatory problems related to manufacturing large scale of GT products, including those aspects of quality, safety and efficacy assessment regulated by the law for manufacturing medicinal products.



Preclinical research

The Legislative Decrees n° 91/93 and n° 92/93 (implementing the EC Directives 90/219/EEC and 90/220/EEC) respectively regulate the confined use and deliberate release of GMOs. The Ministry of Health (Department of Prevention) authorizes separately the facility (laboratory, animal house) where the work with GMOs is intended to be carried and the operation proposed upon evaluation and approval of two specific dossiers (available on the web site www.iss.it). The "Guide to the users and to the producers of GT products" released by the National Committee on Biosafety and Biotechnology provides guidelines applying to the pharmacological, toxicological and immunological studies in animals, and considers the ethical aspects associated with the use of animal models for GT purposes.



Manufacture

GMP has to be applied to all phases of GT studies. The above mentioned guidelines suggested that a partial and temporary limited release to the GMP is acceptable on a case by case basis, in the preparation of small scale GT product to be used in phase I and I/II study unless this will impair the safety of patient, operators or environment. In any case structures manufacturing GT products must have an internal quality control (QC) and external quality assessment (QA), must operate with validated standard procedures within dedicated facilities and provide assessment for the different levels of responsibility.



Clinical trials

GT clinical trials are regulated by the Ministerial Act, July 10th, 1997 and Legislative Decree, August 18th, 1997, aimed at implementing the CPMP/ICH 135/1996 and defining procedures for GCP application. GT products are considered "new drugs" and according to the Italian regulation on Clinical Trials the activation of this type of trial requires a) the notification/authorization from the Ministry of Health; b) the scientific opinion from the ISS; c) the opinion of Local Ethic Committee. The list of documentation necessary for the evaluation and authorization of a clinical protocol is provided by the "Guidelines on GT clinical trials" (1996) and "Guidelines for phase I/II clinical trials of Somatic Cell therapy" (1997) (available on the web www.iss.it). The confined use of the GMO to be used as GT product and the facility where the patient will be treated will have to be notified and approved, as well as the preclinical evaluation of safety, efficacy and tolerability of the same product.



Marketing authorization

The procedures for marketing authorization are centralized and released through the EMEA. At national level the Ministry of Health is the responsible authority through the "Commissione Unica del Farmaco-CUF"



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The Netherlands

Dr Reinder Bolhuis and Dr Huub Schellekens - 1999



Definition and General Comments

All work with genetically modified organisms are regulated by a special part of the Law for the Management of the Environment (Besluit GMOs van de Wet Milieubeheer). For clinical application of gene therapy a permit is needed from the CEMO, the committee on medical experimentation. In addition the Inspector for Public Health has ruled that gene therapy has to be performed under the rule of GLP, GMP or GCP.

The Dutch Government has issued a ban on human germ line therapy.



Preclinical research

Work with GGO within containment can only be performed when the facility has a permit from the Municipal authorities in which the laboratories and rooms are described where work with GMOs is permitted.

In addition, for every project a permit is needed from the Ministry of the Environment on basis of the Ministerial Regulation ("Ministeriële Regeling") which is the national translation of the Council Directive 90/220. The Ministry of the Environment may seek advice from the COGEM, the committee on genetic modification. The COGEM also issues detailed Guidelines, which are in essence also part of the Ministerial Regulations.

Under these regulations the institute where work is being carried out should have a detailed administrative system in which all responsibilities are described, all work instructions are available, a register of responsible scientist and laboratory log books on the work performed. The director of the institute has to appoint a biological safety officer, who supervise all work. Also a responsible scientist has to be appointed for every project. Work can only be performed by qualified and trained personnel.

If animals are involved not only the GMOs rules apply but also the Law on Animal experimentation. If the works involves the production of genetically modified animals a permit is needed from the Minister of Agriculture.



Manufacture

Also for manufacture the permits from the Municipal Authorities (for the facilities) and of the Ministry for the Environment are necessary.

Also the rules for GMP have to be applied by order of the Inspector for Public Health.



Clinical trial

Also for clinical trials the rules for GMOs apply. Because clinical trials are considered introduction in the Environment no permit is needed for a public procedure which includes the possibility of objections by parties involved. The Minister of the Environment consults for every protocol the COGEM. The evaluation is performed by the Medical Subcommittee of the COGEM which involves all other authorities in the Netherlands like the Health Council, the Health Inspectorate, etc. The committee usually organizes hearings with the clinicians and, or companies involved.

Starting May 1, 1999 also a permit is necessary from the CEMO. The CEMO also organizes hearings usually combined with hearings of the medical subcommittee of the COGEM to avoid redundant questions, although the scope of the two committees are different. The COGEM evaluates the safety for the environment, but this has a lot of overlap with the patient safety which is one of the main issues of the CEMO. The CEMO also considers ethical questions, patient information, insurance issues, etc. Clinical trials can only start after permission is granted by the CEMO and the minister of the Environment. The Inspector of Public Health also ordered the application of GCP in clinical trials with gene therapy. In addition the local ethical committees of the hospital(s) involved has to grant permission.



Marketing authorization

Also for the Netherlands the EMEA procedure for marketing authorization is mandatory.



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Norway

Pr Ola Myklebost - January 1999



Definition and General Comments

The definition of gene therapy is at present under scrutiny. It has been suggested that treatment with synthetic nucleic acids without the ability to replicate or integrate should not be classified as gene therapy. The same might apply to DNA vaccination. Therapy modifying the germ line is prohibited.



Preclinical Research

Preclinical research, on cell cultures or in small animals, is regulated under the Act on Gene Technology, which requires a certification of laboratories for contained use. For GMOs that are of interest for gene therapy, this is a rapid process, which causes little problems for the investigators.

 **Manufacture**

As no Norwegian companies at present manufacture gene therapy reagents for clinical use we have no relevant experience. Reagents would have to be produced abroad.

 **Clinical trial**

Clinical trials need approval from regional ethics committees for medicine, but this is not required by law. The gene therapy agent has, like other medicines, to be approved by the Norwegian Medicine Control Authority, and gene therapy trial are required by the Act on Medical Application of biotechnology to be approved by the Norwegian Board of Health.

 **Marketing authorization**

Marketing authorization is given by the Norwegian Medicine Control Authority.

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 **Preclinical research**

Implementation of EC-Directives (contained use EC 90/219 and deliberate release EC 90/220) relating to regulation of GMOs are under the Authority of the Ministry of Environment. Whenever applying to preclinical research, the opinion of the Ministry of Health is mandatory and binding. The Biosafety rules applied either to animal or human experimentation includes bioethics considerations.

 **Manufacture**

Again, implementation of contained use is placed under the control of the Ministry of Environment. GLP and GMP requirements are formally approved by the Instituto do Farmaco e do Medicamento (INFARMED) which is a General Directorate inside the the Ministry of Health. Technical inspection is placed under the Instituto Português da Qualidade (IPQ)) which is a General Directorate inside the Ministry of Economy. Materials, methods and facilities used have to be extensively described and have to be accredited by the rulling Boards appointed by the Ministry of Health as well as by the General Direction of Pharmacy and Medical Devices (Ref: Equipamento médico pesado Decreto-Lei n° 95/95 de 9 de Maio).

APIFARMA is a professional Association of pharmaceutical producers which has no binding power in these matters.

 **Clinical trial**

Clinical research projects in Portugal need to be authorized by the Ministry of Health assisted by the National Bioethics Committees nominated by the government (the members of these Committees are by far recruited among qualified scientists incorporated in the Ministry of Education) (ref: Comissoes de Etica para a saúde Decreto-Lei n° 97/95 de 10 de Maio).

The Biosafety rules applied to human experimentation includes bioethics considerations as well as clinical relevance, therapeutic efficacy and informed consent of the patients and families. All experimentation should specifically refer to the duration of the procedure/s, medications involved, level of patient risk and clinical follow-up by the Institution in charge as well as the qualifications of the consulting doctors of medicine and of the principal investigator.

The facilities of the Hospitals and Institutions (Ministry of Health and Ministry of Education) endorsing the trials in question should be formally and regularly inspected by the Committees nominated by the Ministry of Science and Technology and are subject to the regulations issued by the Public Health Authorities (Ministry of Health) as well as by the Epidemiologic Departments such as the National Institutes of Health (Ministry of Health).

All the ongoing clinical trials which as above pointed do not apply so far to genetically modified organisms have to comply with the general directives of the European Commission.

 **Marketing authorization**

In the European Union, this level of regulation is to be covered by the centralized procedure for marketing authorization through the European Medicines Evaluation Agency (EMEA), entering into force on 01.07.95, and involving a decision binding on all Member States of the European Union (Regulation [EEC] Nr. 2309/93). The CPMP (Committee for Proprietary Medicinal Products) has adopted guidance to support marketing authorization of gene therapy products (December 1994: III/5863/93 Final); these guidelines are currently being revised (please refer to EMEA-web-site).

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 **Portugal**

*Updated as for 12/1998,
Pr Maria Cristina Rosamond Pinto adapted by
Euregenethy Coordinator and Pr Manuel J.T. Carrondo*

 **Definition and General Comments**

In Portugal there are no formal gene therapy regulations or laws. No GT trials are listed within the scope of the research projects funded by National Institutions like the JNICT (National Board of Research, Science and Technology). This Institution is now under the jurisdiction of the Ministry of Sciences, Industry and Technology created by the Parliament since the Socialist Party won the elections in 1993/94. It is expected that soon this Ministry will come up with regulations concerning the above mentioned subject.

The National Ethics Committees have already pronounced against gene therapy concerning the human germ lines although no formal decrees have been released regarding gene therapy in somatic cells.



Spain

Dr Jose M. Amate-Blanco - 01/1999
adapted by Euregenethy Coordinator



Definition and General Comments

Several Spanish teams are carrying out basic investigations aiming at gene therapy on experimental models. However Spanish experience at the clinical level is very short. No specific regulation has been implemented. In fact it has been possible to act so far under general legislation regulating a variety of existing health interventions. This legislation mainly consists in a transposition of EEC Directives.

Therefore gene therapy interventions follow the general legal frame that regulates the development of any health technology. Products under use are being considered high technology drugs to which the pharmaceutical regulation applies.

Health technologies assessment is placed under the Health General Law . This evaluation is guided to determine the health, social and economic impacts of the new technology under scrutiny, in comparison with alternative interventions. This action is regulated by the Royal Decree 63/1995 , on the organisation of health services provided by the National Health System in agreement with the provisions of article 110 of the Law 14/1986, the General Law of Health.

According to the Royal Decree 63/1995, the Ministry of Health and Consumer Affairs may authorise the use of certain techniques or procedures for a limited time only using appropriate guarantees.

As a whole regulation covers the following aspects:



Preclinical research

1. *GMOs*: EC 90/219 (Contained Use) and EC 90/220 (Deliberate Release) are transposed to Spanish regulation by Law 15/1994 and Royal Decree 951/1997. They are applicable to facilities and activities but not to investigations at very short scales. This field is under jurisdiction of Ministry of Environmental Affairs.

2. *Investigational products*. Chemical or biological entities that are not active ingredients of pharmaceutical specialities registered in Spain need to obtain the assessment of product under clinical research. Towards this end, preclinical studies are required in order to establish its pharmacological and toxicological profile, before products would be used in clinical research.



Manufacture

The samples used in clinical trials have to be performed according to Good Manufacturing Practice standards (EEC guidelines). Quality Assurance of industrial manufacture of medicines is ruled by the Royal Decree 1564/1992. If the samples are imported products, the Technical Director will endorse their quality by adopting the appropriate inspection and control operations. Likewise, he/she will send the corresponding authorities samples of the products which are to be used in the clinical trial, if so requested.



Clinical trial

1. *Clinical trials may only be carried out all the following principles have been complied with:*

- 1.1. The pre-clinical data about the product under study are reasonably sufficient to guarantee that risks to the subjects on whom the trial is conducted are admissible.
- 1.2. The study is based on disposable present data, and the research represents, or may represent, an improvement of scientific knowledge about humans or an improvement of human health, and its design should minimise the risk to the subjects.
- 1.3. The interest of information being sought justifies the risks to which subjects taking part in the clinical trial are exposed.

2. *Clinical trials with a new drug*

Clinical Trials (CT) are regulated by the Royal Decree 561/1993. CT must be authorised by General Directorate of Pharmacy and Medical Devices (GDP and MD) with previous assessment by ethics committee. The Ethic Committees of Clinical Research will be accredited by the competent Health Regional Authority in each Autonomous Community, that has to communicate it to the Ministry of Health and Consumer Affairs. Clinical trials will be performed respectfully in relation with fundamental human rights and ethical postulates affecting biomedical research on humans, following the contents of the declaration of Helsinki and its successive updates. It will be necessary to obtain and document informed consent, freely stated, of each subject of the study before he/she is included.

3. *Covering by National Health System, prescription and dispensing regimes*

These regimes are stated according to the Royal Decree 83/1993 and the Royal Decree 767/1993. Last year, Inter-territorial Board of the National Health System opened a prioritisation process of around 150 health technologies previously listed. Gene therapy products were on above mentioned list. Nevertheless, the opinion currently prevailing is that Gene Therapies remains a basic investigation and that it is too early to discuss its adoption by health attendance of National Health System, outside the frame of specific clinical trials.



Marketing authorization

In the European Union, this level of regulation is to be covered by the centralized procedure for marketing authorization through the European Medicines Evaluation Agency (EMA), entering into force on 01.07.95, and involving a decision binding on all Member States of the European Union (Regulation [EEC] Nr. 2309/93). The CPMP (Committee for Proprietary Medicinal Products) has adopted guidance to support marketing authorization of gene therapy products (December 1994: III/5863/93 Final) ; these guidelines are currently being revised.



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3. *On medicines and clinical trials*: Law 25/1990, Royal Decree 561/1993.
4. *On Health benefits*: Law 25/1990, Law 14/1986, Royal Decree 63/1995.



Pr Gösta Gahrton - April 1999

Definition and General comments

Gene therapy in Sweden is mainly regulated by the Environmental Code (SFS 1998:808) and its ordinances. In practically all respects the regulation follows the Council Directives 90/219/EEC on contained use and 90/220/EEC on deliberate release of genetically modified organisms (GMOs). Amendments of the Swedish regulation, based on Directive (98/81/EC) amending 90/219/EEC is in progress.

Genetically modified micro-organisms (GMOs) are classified as group I GMOs or Group II GMOs. Group I GMOs are of low risk for damage on human health and the environment, while Group II GMOs are those which do not belong to Group I. Group II GMOs are also classified in safety class 1-4 as biological agents according to risk for human health. Class 1 agents are not likely to cause human infection and class 4 are the most dangerous agents. Products for gene therapy have so far been classified as Group II. The National Board of Occupational Safety and Health defines criteria for classification in group and safety class. GMOs in clinical trials have so far been performed as contained use as defined in the Directives 90/219/EEC. If a clinical trial is performed without containment, as field trial, it would need consent for deliberate release of GMOs, except placing food or pharmaceuticals on the market. No application has so far been supplied.

Preclinical research

Preclinical research is regulated by the above mentioned Environmental Code (SFS 1998:808) and its ordinances, among them SFS 1998:945 amending SFS 1994:901 on GMOs. Preclinical research is usually regarded as type A activity according to Directive 90/219/EEC (research on small scale). Notification to the National Board of Occupational Safety and Health is required. The facility for the research must have a permission. The ordinance concerning Biological Agents (AFS 1997:12) applied as well. If the preclinical research involves animal work permission should also be obtained from the Ethical Committee for Research on Animals.

Manufacture

The manufacture of gene therapy products for clinical use, *i.e.* GMOs like retroviral vectors, etc. would be regarded as type B activities (large scale industrial or commercial activities). The manufacture should be made in GMP facilities. Permission is needed from the National Board of Occupational Safety and Health as well as from the Medical Products Agency.

Clinical trials

Permission for a clinical trial is obtained from the Medical Products Agency as well as from the Local Ethical Committee. Applications on specific forms are made to both. The time frame from sending the application to decision is about 2-3 months. Notification to the National Board of Occupational Health must be made. The conditions are otherwise the same as for preclinical research.

Marketing authorization

Marketing authorization is made by the European Commission and follows EC centralised regulations (EMEA) applying to Gene therapy.

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References

1. Miljöbalken (Environmental Code) (SFS 1998:808).
2. SFS (1998:945). Förordning om ändring av förordningen (1994:901).



Dr Karoline Dorsch-Häsler - 01/1999

Definitions and General Comments

In Switzerland, neither a new gene law nor a specific ordinance on gene therapy has been established. Gene therapy is regulated by several laws, ordinances and regulations. In addition, a law on medicinal products (Heilmittelgesetz) is in preparation which will also cover gene therapy. This law should come into force by the year 2000. Therapy germline cells is prohibited in Switzerland according to Article 24novles of the Federal Constitution.

A clinical gene therapy trial has to be assessed by the ethics committee and by the Swiss Biosafety Committee. In addition, the Federal Office of Public Health and the Intercantonal Office for Control of Medicines have to be notified of the trial. Currently, US and EU Guidelines are applied for the assessment of the biosafety of the gene therapy products.

Definition: Gene therapy is defined as a therapeutic or prophylactic change of the genetic program of living cells [Ref 1]. The following compounds can be involved *in vivo* as well as *ex vivo* applications : Genetically modified human or animal somatic cells, viral vectors, and nucleic acids, either naked, as a complex or encapsulated.

Preclinical research

Experimental work in gene therapy, *i.e.*, work with genetically modified and pathogenic organisms is regulated by the Federal Law on Protection of the Environment and the Law of Epidemics [Ref 2]. Ordinances containing a detailed description of the notification procedures, biosafety, requirements and responsibilities by the various authorities will come into force in 1999 :

- the Ordinance on the Contained Use of Organisms
- the Ordinance on the Protection of Workers against Risks Originating from intended or Unintended Use of Microorganisms [Ref 3].

The regulations are harmonized with the Council Directives of the European Union 90/219/EEC and 90/679/EEC respectively.

Notification of Experiments: The Swiss Agency for Environment, Forests and Landscape or the Federal Office of Public Health, Berne (see below) have to be notified of experiments in preclinical research.

Laboratory approval for research: is given by the competent authorities of the cantons (states).

The Swiss Expert Committee for Biosafety (Eidgenössische Fachkommission für biologische Sicherheit, EFBS ; Commission Fédérale d'experts pour la sécurité biologique, CFSB) [Ref 4], instituted by the Swiss Federal Council in 1997, advises federal and cantonal authorities on questions regarding biosafety.

Manufacture

During manufacture of gene therapy products *Good Manufacturing Practice* (GMP) according to the Pharmaceutical Inspection Convention (PIC) [Ref 5] or the *European Guide to Good Manufacturing Practice* (1997) have to be implemented. Additional guidance is provided by the European Agency for the Evaluation of Medicinal Products (EMA), *Safety Studies for Gene Therapy Vectors* [Ref 6]. For testing, regulations for Good Laboratory Practice (GLP) apply (*Principles of Good Laboratory Practice*, OECD, 1998).

Clinical Trials

Regulations : Trials with gene therapy products defined as immunobiological products are regulated by the *Ordinance on Clinical Trials with Immunobiological Products* (1996, issued by the Federal Office of Public Health, Ref 7) for the other cases the *Regulation on Clinical Trials with Medicinal Products* (1993, issued by the Intercantonal Office for Control of Medicines, Ref 8) applies. For clinical trials, the rules of Good Clinical Practice (GCP) have to be followed (defined in Ref 8). In addition, the Ordinance on the Use of Organisms in the Environment [Ref 3], corresponding to Council Directive 90/220/EEC is applied for the assessment of the biosafety of environmental data.

Biosafety : Currently, questions regarding biological safety in gene therapy trials are still dealt with the *Swiss Interdisciplinary Committee for Biological Safety in Research and Technology* (SKBS/CSSB), set up by the Swiss Academy for Medical Sciences, but this task will be taken over by the EFBS/CFSB in 1999. A gene therapy proposal submitted to the SKBS/CSSB has to conform essentially with the FDA Points to consider in human somatic cell therapy and gene therapy (1991 and changes added in the following years, Ref 9). The Biosafety Committee will consider a submitted protocol within three months.

Ethics committee : In addition, positive appraisal is required by a *local ethics committee* or by the Supraregional Ethical Commission (Ueberregionale Ethische Kommission für Klinische Forschung UREK) in case of absence of a local ethics committee. The Medical Ethical Guidelines on Somatic Gene Therapy of Humans (issued in 1998 by the Swiss Academy for Medical Sciences) [Ref 1] form the basis for the appraisal by the ethical committees.

Notification : Either the Federal Office of Public Health (if the product used can be defined as immunobiological product) or the Intercantonal Office for Control of Medicines have to be notified of a gene therapy trial. A trial can be initiated 30 days following notification provided that the local ethical committee and the Biosafety Committee (SKBS/CSSB) have given positive appraisal.

Marketing authorization

Marketing authorization will be given by the Federal Office for Public Health and will be regulated by the Ordinance on Immunobiological Products [Ref 10] for immunobiological products, or by the Intercantonal Office for Control of Medicines.

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United-Kingdom

Dr Richard Vile 02/1999

adapted by Eurenethy Coordinator and revised 05/1999



Definition and General Comments

The 1992 report of the Committee on the Ethics of Gene Therapy (the Clothier Committee) recommended that gene therapy (genetic engineering in humans) should be limited to life threatening diseases or disorders.

To oversee and implement this GTAC, a non-statutory body was established in 1993. GTAC advises on the ethical acceptability of proposals for gene therapy research on humans taking account of the scientific merits and the potential benefits and risks, and provides advice to UK health Ministers on developments in gene therapy research.

The primary concern of GTAC is whether each research proposal meets accepted ethical criteria for research on human subjects. This includes both therapeutic and non-therapeutic research. GTAC approval must be obtained before somatic cell gene therapy (*i.e.* on any cell other than the sperm or egg cells) or gene transfer research is conducted on human subjects. GTAC will not, at present, consider proposals for germ line cell (egg or sperm) gene therapy research on human subjects.

GTAC is a consultative Body of Advisers the approval of which is not binding under a specific law. The Medicines Control Agency, the Health and

Safety Executive and the Department of the Environment, hold statutory responsibilities. In any case, final approval by MCA is not likely to be released without prior and favourable acceptance by GTAC.

Definitions of naked nucleic acid, complexed nucleic acid, replication-deficient viruses of genetically modified cells are provided in GTAC Guidelines (available on this web-site and GTAC web-site).

Preclinical Research

In vitro and *in vivo* studies using appropriate models and relevant animal species should be designed to show that the gene is expressed at the appropriate site, in the appropriate cells at an appropriate level (extent and duration) and that functional activity is realized. It is important to develop adequate methods for monitoring whether appropriate expression occurs. Reporter genes may be helpful to assess the transgene delivery into target cells and its subsequent expression. Strategies to confer specific tissue tropism/targeting of the gene therapy product to the desired target site should be evaluated in relevant animal models.

A rationale should be given for the proposed dosing regimen in the clinical studies if repeated administration is envisaged.

Implementation of EC Directives on Genetically Modified Organisms (EC 219/90 and EC 220/90) is placed under the Health and Safety Executive and the Department of Environment, respectively.

In May 1999, the UK government announced the creation of a Human Genetics Commission (HGC) as part of a series of measures to help the biotechnology industry to develop and demonstrate its potential benefits in the face of the current concern about genetically modified food. The HGC is to advise on biotech applications in healthcare and the impact of human genetics on people's lives. The Commission should take broad, long-term view of technological developments.

Manufacture

Requirements relating to establishments in which biological products are manufactured (*e.g.* Directive 91/536/EEC on GMP and EC Directive 90/219/EEC on the contained use of genetically modified micro-organisms) will apply to the manufacture of gene therapy products as well several of the general recommendations for the quality control of biological products.

Appropriate attention needs to be given to the quality of all reagents used in production: specifications for these are to be included in documentation and they should comply with any relevant EC recommendations (*e.g.* Note for guidance on BSE). It is undesirable to use in production agents which are known to provoke sensitivity in certain individuals, such as, for example penicillin or other β -lactam antibiotics.

(a) Attention will be given to the following: where possible, evidence should be obtained that the correct nucleotide sequence, or that at least the correct coding capacity, has been made and that this has been stably maintained during the amplification steps before transfer and that the sequence/coding capacity remains unmodified following transfer. (b) In most instances the genetic material (nucleic acid) involved will be ligated into appropriate plasmids or cassettes having promoters which regulate its expressions. The resulting expression constructs may be complexed. In these cases, all components of the final transfer vector should be thoroughly characterized. (c) Virus vectors raise particular issues regarding manufacture and safety. Viral nucleic acid sequences known to be associated with pathological effects should be deleted. The aim should be the construction of packaging cell lines which make the production of replication competent (infectious) virus(es) by recombination with the viral genome of the gene transfer vector used impossible. (d) In some cases, genetically-modified somatic cells might themselves be perceived to be products. (e) Potential impurities in the final product will be influenced by the choice of manufacturing procedure and the purification processes, where applicable, must be shown to be capable of removing them. (f) Procedures to ensure consistency of production conditions as well as of the final product are imperative. (g) Scale-up of culture and/or purification occurs as laboratory developments progress to full scale commercial production, and this may have significant consequences for the quality of the product including effects on its biochemical and biological properties, and thus implications for control testing.

Clinical trials

GTAC. In November 1993, the UK Government established the Gene Therapy Advisory Committee (GTAC) whose terms of reference are:

1. to consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds taking account of the scientific merit and the potential benefits and risks of the protocol;
2. to work with other agencies which have responsibilities in the field, including local research ethics committees and agencies with statutory responsibilities, the Medicine Control Agency, the Health and Safety Executive, and the Department of the Environment;
3. to provide advice to United Kingdom Health Ministers on developments in gene therapy research and their implications. Approval by GTAC must be obtained before gene therapy or gene transfer research is conducted on human subjects. This is based on a case by case review. One of the Committee's first priorities has been the production of guidance which have been published as "Guidance on Making Proposals to conduct Gene Therapy Research on Human Subjects".

Local research ethics committee (LREC). 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). Gene therapy research is no different to any other class of research. An LREC may also advice on studies carried out by private companies, the Medical Research Council or Universities. The final judgement of GTAC is always transmitted to LRECs as well as the proposers.

MCA. The statutory authority responsible for the regulation of new medicinal products in the UK is the Medicine Control Agency (MCA) which operates in a very similar way to the FDA. Like the FDA the review process occurs on a case by case basis within a general framework of principles. Before an investigator can start a trial they must apply for either a Clinical Certificate (CTC), a Clinical Trials Exemption (CTX) or a Doctors and Dentist Exemption (DDX). For each of these data are required to support the application, although the requirements for DDX exemption have traditionally been minimal. In particular, the following information is needed specifically for gene therapy trials: (1) Information on the handling and preparation of the gene therapy product; (2) Pre-clinical testing including formulation primary and secondary pharmacology, immunological problems, insertional mutagenesis and pathogenicity; (3) Clinical information: rationale and assessment of possible risks.

Marketing authorization

The deliberate release of medicinal products containing or consisting of GMOs for the purpose of placing them on the market falls within the scope of Council regulation (EEC) 2309/93, which provides for a specific environmental risk assessment similar to that laid down in the Directive 90/220/EEC. Thus, in its opinion on applications for marketing authorization of such medicinal products, the CPMP shall ensure that all appropriate deliberate release or placing on the market of genetically modified organisms.

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References

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June 29-30 1999 in Brussels

Targeted Workshop on Regulation of Gene Therapy. Closed Meeting. This forum will gather for the first time EU-officials, a majority of officers in charge with the review of gene therapy files in each European country, representatives of the EMEA, CPMP and FDA, Euregenethy partnership together with a panel of selected experts including members of the European Society of Gene Therapy (ESGT), targeted companies, Bioethics', patients' and GCP's panels. The programme is established in order to :

- 1) Favour interactions between regulators and users ;
- 2) Highlight difficulties encountered so far in various countries applying to a variety of scientific issues ;
- 3) Initiate a reflexion on potential improvements with a spirit of concertation.

June 9-11 2000 in Paris

Multidisciplinary forum on Regulation of Gene Therapy conceptualized as "extended audience"; to be organised in case interaction proves constructive during June 1999 Targeted Workshop.

This second meeting will provide an opportunity for enhanced interaction between all interested parties (including the audience of 1999-workshop). Scientists will be consulted on the regulatory implications of novel technologies currently being developed (*i.e.* biosafety risks and suggestions applying to the assessment/containment of new gene transfer vectors)(Call for abstracts including regulatory and safety aspects). This meeting aims at issuing an accurate set of recommendations following European-wide concertation.

This might ultimately help decision-making by regulatory authorities.

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