

□ Gene Therapy in Germany and in Europe: Regulatory Issues

In the European Union the marketing authorization for gene therapy products is obtained following the centralized procedure for marketing authorization via the European Agency for Evaluation of Medicinal Products (EMA). For evaluation and review of clinical protocols there is no authority established at the level of the European Union. The different member states have settled on an ad hoc review process on different levels, i.e. national regulatory agencies, local or national ethics committees and others. The following paper gives an overview on the regulatory issues of gene

therapy in Europe focusing mainly on the specific situation in Germany. The view of the regulatory authorities is compared with the perspective of a pharmaceutical company. Additionally key features of the regulations in the UK and France are briefly outlined.

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DEFINITION

Somatic gene therapy drugs for human use either consist of or contain genetically modified cells or are intended to be used for the genetic modification *in vivo* of human or animal cells (see Figure 1).

BIOLOGICAL DRUGS RELATED TO GENE THERAPEUTICS

Some of the properties of gene therapy drugs relate to those known from live virus vaccines [1–3,13,19,26–28]. These vaccines may also modify cells, mutate or recombine similar to the recombination of viral vectors in their packaging cells, or spread to third party individuals. Moreover, they induce expression of foreign proteins within the treated organism like the expression constructs transferred during gene therapy. Of course, live virus vaccines are not gene therapy products. They were developed long before the idea of genetic modification of organisms for therapeutic purposes was developed. In addition, even the use of live recombinant vaccines carrying cytokine genes in order to increase the immunogenicity of the expressed antigens of the pathogen, once they are to be used, will probably be covered by regulations on vaccines.

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“live virus vaccines are not gene therapy products”

A number of vaccines, such as genetically modified autologous or heterologous tumour cells currently tested in clinical trials as tumour vaccines for the treatment of cancer patients or DNA vaccines developed to protect against infectious diseases such as influenza or malaria, are also gene therapy drugs. These will probably be more effectively covered by gene therapy guidelines than by guidelines for live virus vaccines as developed for individual vaccines. This relates to the specific quality and safety aspects relevant for the production of DNA, vectors or cells used, and the specific gene therapy applications which are less related or completely different from those of recombinant live vaccines.

Cell marking protocols also involve the use of gene therapy drugs according to the definition. Expression constructs used for cell marking may preferably be termed transfer or packaging constructs because they may not always have to encompass cDNAs to be expressed but sequence tags to mark the cell with DNA that can easily be detected, even in the presence of a large amount of unmarked cell DNA.

Nonetheless, there is a number of medicinal products which share certain features with some of the gene therapy drugs that are being developed. For example, non-human or primate organs may in the future be genetically modified to abrogate their physiological rejection by the human organism, and may then be used as organ transplants in human beings. These xeno-organs will contain genetically modified cells and, therefore, have some characteristics reminiscent of gene therapy drugs. The distinction between genetically modified organ transplants and gene therapy drugs is mostly theoretical and neither of current practical nor regulatory concern. The safe use of xenogeneic organs will most likely be dealt with by specific regulations. Some risks related to the genetic mod-

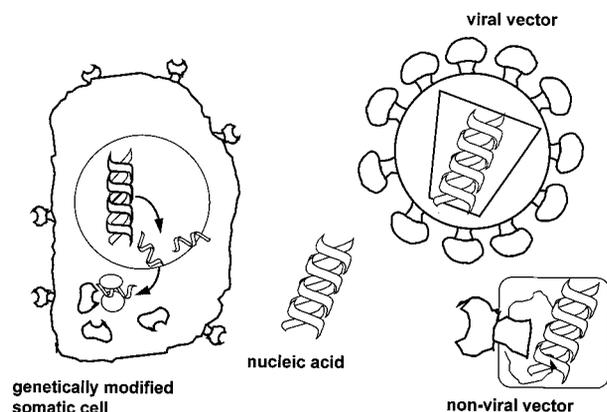


Figure 1. Gene therapy drugs

ification of the cells of the xenogeneic organ may, however, be more effectively dealt with by applying guidelines for specific gene therapy products. Given the prospect of efficient homologous recombination into specific chromosomal sites, small nucleic acid fragments may in the future be used as gene therapy drugs to convert point mutated alleles of target genes against their wild type counterparts. Unrelated to gene therapy products, anti-sense RNAs and small DNA fragments capable of triple helix formation will also be used in molecular medicine for the temporary suppression of gene expression. According to the European Note for Guidance 'Gene Therapy Products—Quality Aspects in the Production of Vectors and Genetically Modified Somatic Cells' these drugs are not included in the definition of gene therapy products most likely because they very transiently modify the pattern of gene expression in the absence of any true genetic modification of the cells. More importantly, they impose pharmacological and safety issues dissimilar from gene therapy products.

“All of these drugs harbour common risks including the genetic modification of the germ line”

POTENTIAL RISKS OF GENE THERAPY

The common feature of gene therapy products is the modification of human somatic cells *in vivo* or the transfer of genetically modified autologous, allogeneic or xenogeneic cells. A comparable risk/benefit assessment has to be made for gene therapy vectors or DNA applied *in vivo* and for somatic cell therapeutics which are prepared by modification of human or animal cells *ex vivo* before they are introduced into the organisms [2,5,24,27]. All of these drugs harbour common risks including the genetic modification of the germ line, the spread of the transferred expression constructs to other physiological sites not intended to be modified and the possible genetic modifications of third party individuals by inadvertent vector spread. Theoretical examples of such risks include the infection of the treated organism by a replication competent virus, introduced for example as a result of insufficient testing of the absence of such viruses from the vectors used for somatic cell modification. Replication competent viruses may not only contaminate viral vectors intended to be used *in vivo* or used for the genetic modification of cells *ex vivo*. They may also contaminate

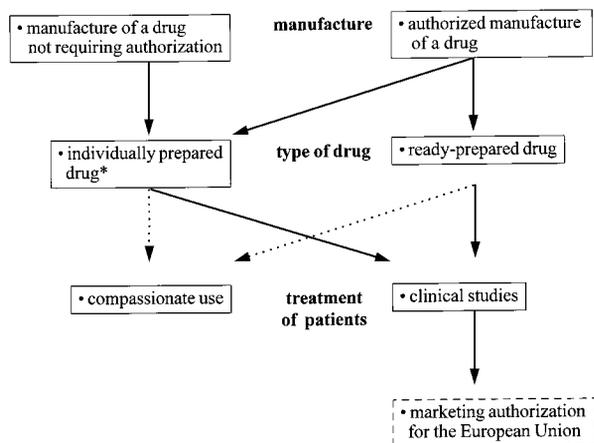


Figure 2. Manufacture and use of gene therapy drugs in Germany. * Individually prepared drugs do not require marketing authorization.

non-viral vectors such as complexes used for transfection, as they contain an admixture of inactivated adenoviruses which may happen to be incompletely inactivated during the preparation of larger amounts of the gene therapy drug. Spread of the expression constructs introduced at defined sites into the organism is also undesirable and may promote the risk of germ line modification. The expression of the biologically active molecule in an inappropriate organ may also have unintended pharmacological or toxicological consequences [7–11,13,15,18,20–23,27,28]. Thus, all gene therapy drugs have certain risks in common. These risks can, however, be reduced to a minimum by rigorous testing of the quality and safety of the drugs prior to their use.

REGULATIONS IN GERMANY

Pre-clinical research and development

Vectors, DNA or modified cells which may later be used as gene therapy drugs can be constructed and analyzed in laboratories approved according to the German Gene Technology Law ('GenTG') by the competent authorities in each federal German state ('Bundesland') [4,12,14,16,17,32]. Pre-clinical data including analyses of the pharmacological-toxicological characteristics are generated in gene laboratories or approved animal facilities.

Once DNA, vectors or modified cells are prepared as ingredients of gene therapy drugs or as the drugs themselves, the manufacture may have to be authorized. Alternatively, the competent authority of the federal German state has to be notified (Figure 2). Gene therapy products may be prepared

as individually or ready-prepared (finished) drugs [29–31]. In both cases, patients may be treated during a clinical trial or in compassionate use regimens. There is a considerable body of regulations including the German Drug Law ('Arzneimittelgesetz') protecting the patients during clinical trials. A finished drug, also termed proprietary medicinal product, e.g. an adenoviral vector for the treatment of patients suffering from cystic fibrosis, requires marketing authorization. It is also conceivable that users other than the manufacturer will be provided with individually prepared drugs. These drugs will have to be manufactured in authorized facilities, but it is not necessary to obtain marketing authorization. More detailed comments on the regulatory framework of gene therapy in Germany are listed below. A general outline of points to consider for the manufacture of and the treatment of patients with gene therapy drugs in Germany is given in Tables 1 and 2.

In order to allow standard treatment of patients with a gene therapy drug, there are currently two typical approaches imaginable. For example, autologous recombinant tumour vaccines are gene therapy drugs which are currently prepared (with or without the requirement of obtaining manufacturing authorization) in specialized departments of German university clinics individually for each patient (Figure 2). After testing these drugs in clinical studies, standard treatment of patients would not only be legal, but may also be paid by the health insurances, if efficacy has been demonstrated during clinical trials. It may legally be possible to treat patients with individually prepared drugs without having undertaken any clinical trial. The second approach (Figure 2) would encompass the manufacture of a finished drug, most likely by a company. The manufacture would thus have to be authorized by the competent authority of the federal German state or the member state of the European Union (EU) from where the drug would be imported. Alternatively, if the drug is not manufactured in a member state of the European Community or in a contracting state of the Agreement of the European Market, an import license would have to be obtained from the competent authority of the federal German state. Data supporting an application for marketing authorization for the EU (see below) would then be collected during clinical trials.

Regulation of pre-clinical research and development of gene therapy drugs by the Gene Law

Most gene therapy laboratories in Germany have a long-term history of research in molecular biology

Table 1. Laws, directives and guidelines to consider for the manufacture of and the treatment of patients with gene therapy drugs in Germany

(A)	Manufacture
<i>Authorized</i>	<i>Not requiring authorization</i>
	<i>Drug Law (AMG)</i>
<ul style="list-style-type: none"> - Application for manufacturing authorization to competent authority of the federal German state (§ 13 AMG) 	<ul style="list-style-type: none"> - Notification of the competent authority of the federal German state (§ 67 AMG)
<ul style="list-style-type: none"> - Inspection of the production facility by the competent authority is possible 	
	<i>Gene Law (GenTG)</i>
<ul style="list-style-type: none"> - Notification of/approval by the competent authority of the federal German state of safety level 1–3 gene laboratories and the operations carried out 	
	<i>Further directives and guidelines applicable</i>
<ul style="list-style-type: none"> - German directive 'Operation Ordinance for Pharmaceutical Entrepreneurs (PharmBetrV)' implementing quality control, GMP etc. 	- ./.
<ul style="list-style-type: none"> - Guidelines on GMP of the WHO, the EC and PIC 	
<ul style="list-style-type: none"> - EC 'Notes for Guidance' on 'Gene Therapy Products', 'Products Derived by Recombinant DNA Technology', 'Virus Validation Studies' 	
(B)	Clinical trial
<i>Finished drugs</i>	<i>Individually prepared drugs</i>
	<i>Drug Law (AMG)</i>
<ul style="list-style-type: none"> - Vote of the competent and independent local ethics committee which may ask advice from the central 'Committee for Somatic Gene Therapy' (formed under the auspices of the Federal Chamber of Physicians) 	
<ul style="list-style-type: none"> - Notification of the competent authority of the federal German state (§ 67 AMG) which may supervise the conduct and impact the sites (§ 64 AMG) 	
<ul style="list-style-type: none"> - Presentation of the pharmacological–toxicological data, the study protocol, the names of the investigators, the study sites and the vote of the local ethics committee to the competent federal higher authority (Paul-Ehrlich-Institut or the Federal Institute for Drugs and Medical Devices) 	
<ul style="list-style-type: none"> - Informed consent of enrolled patients (§ 40 AMG) 	
<ul style="list-style-type: none"> - Insurance (§ 40 AMG) 	
<ul style="list-style-type: none"> - Further legal restrictions (§ 40, 41 AMG) 	
<ul style="list-style-type: none"> - German directive 'Arzneimittelprüfrichtlinien' 	- ./.
	<i>Gene Law (GenTG)</i>
<ul style="list-style-type: none"> - If the gene therapy product consists of or contains GMOs: notification of/approval by the competent authority of the Bundesland of safety level 1–3 gene laboratories and the operations carried out 	
	<i>Further laws, directives and guidelines applicable</i>
<ul style="list-style-type: none"> - ICH guideline for GCP 	
<ul style="list-style-type: none"> - Implementation of GLP (Annex 1 of § 19 ChemG) 	
(C)	Compassionate use
	<i>Professional Law and Declaration of Helsinki</i>
<ul style="list-style-type: none"> - Vote of the competent local ethics committee which may ask advice from the central 'Committee for Somatic Gene Therapy' (formed under the auspices of the Federal Chamber of Physicians) 	
<ul style="list-style-type: none"> - Informed consent of the enrolled patients 	
	<i>Gene Law (GenTG)</i>
<ul style="list-style-type: none"> - If the gene therapy product contains or consists of GMOs: notification of/approval by the competent authority of the Bundesland of safety level 1–3 laboratories and the operations carried out 	
(D)	Marketing authorization
<ul style="list-style-type: none"> - 'Scientific Advice' by CPMP on issues concerning clinical trials, collection of pre-clinical or other data supporting marketing authorization 	
<ul style="list-style-type: none"> - Obtaining marketing authorization following Council Regulation (EEC) No. 2309/93 	
<ul style="list-style-type: none"> - 'The Rules Governing Medicinal Products in the European Community' 	

Table 2. Directives and guidelines relating to GMP (A) and the quality and safety of gene therapy drugs (B)

Directives relating to GMP

German Directive 'Betriebsverordnung für pharmazeutische Unternehmer (PharmBetrV)' of 8 March 1985 (BGBl. I, S. 546), changed on 9 August 1994 (BGBl. I, S. 2071)

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 (O. J. No L 193 of 17.7.91)

Guidelines relating to GMP

'Guide to Good Manufacturing Practice for Medicinal Products' as well as the supplement 'Manufacture of biological medicinal products for human use' in 'The Rules governing Medicinal Products in the European Community', Volume IV, January 1992; available e.g. via the Bundesanzeiger Verlag, Breite Str. 78-80, 50667 Köln, Tel. +49 221 20290, fax: +49 221 2029278

'Good Manufacturing Practices for Biological Products', WHO Technical Report Series No. 834, S. 20, 1993

'Good Manufacturing Practices for Pharmaceutical Products', WHO Technical Report Series No. 822, S. 14, 1992

German Directive 'Bekanntmachung von ergänzenden Leitlinien zum Leitfaden einer Guten Herstellungspraxis für pharmazeutische Produkte der Pharmazeutischen Inspektions-Convention- PIC-' of August 17, 1993 (BAnz. Nr. 176, S. 9073)

Directives relating to the quality and safety of biological drugs

Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (O. J. No L 147 of 9. 6. 75)

Commission Directive 91/507/EEC of 19 July 1991 modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products (O. J. No L 270 of 26.9.91)

The annex of Council Directive 75/318/EEC in its modified version as in Commission Directive 91/507/EEC led to a novel version of the German Directive 'Arzneimittel-Prüfrichtlinien' ('Bekanntmachung der Neufassung der Allgemeinen Verwaltungsvorschrift zur Anwendung der Arzneimittelprüfrichtlinien' of 5 May 1995 (BAnz. No 96a of 20 May 1995)

'Note for guidance' relating to the quality and safety of gene therapy drugs

'Gene Therapy Products—Quality Aspects in the Production of Vectors and Genetically Modified Somatic Cells', III/5863/93, Commission of the European Community, Directorate—General Industry III/E/3; e.g. available via the 'Office for Official Publication for the European Communities', 2 Rue Mercier, L- 2985 Luxembourg (Tel.: +352 499281, fax: +352 490003)

'Notes for guidance' relating to the quality and safety of drugs for human use

'Production and Quality Control of Medicinal Products Derived by Recombinant DNA Technology', III/3477/92, Commission of the European Community, Directorate—General Industry III/E/3

'Guidelines on the quality, safety and efficacy of medicinal products for human use', in 'The rules governing medicinal products in the European Community', Volume III, January 1989

'Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses', CPMP/268/95, Commission of the European Community, Directorate—General Industry III/E/3

or virology. According to the German Gene Law (which is a transformation of Council Directives 90/219/EEC and 90/220/EEC), experiments in gene therapy involving the use of genetically modified organisms (GMOs) have to be performed in gene

laboratories of safety levels 1–3 used for research, which have been approved of by the competent authority of the federal German state where the laboratory is located (see Table 1). The approval is given only in conjunction with specific lines of

experiments or operations, also termed 'projects', during which defined GMOs are generated. Experiments involving the use of viral vectors derived from retro- and adenoviruses would comply with safety level 2, whereas genetically modified human or animal cells transduced or transfected by the commonly used expression constructs derived from murine leukaemia virus (MLV) would fall under safety level 1. This, of course, is correct under the provision that the cells are not infected by replication competent viruses or harbour functional nucleic acids from organisms known to be pathogenic in humans and that the expression construct itself does not contain nucleic acid sequences of any possible pathogenic potential. When gene therapy drugs are manufactured commercially or in large amounts, the manufacturing sites will have to be registered according to the Gene Law as gene laboratories for commercial use. A list of the safety levels under which organisms used for the generation of GMOs fall is published by the central safety committee termed ZKBS ('Zentrale Kommission für die Biologische Sicherheit') [16].

Research laboratories of safety level 1 are registered by notification of the competent authority of the federal German state prior to the beginning of the work. The legally given time for the completion of gene lab registration for safety levels 2 and 3 is 3 months. In addition to the initial registration of the molecular genetic laboratory and the approval of the initial experiments, all following experimental operations need additional approval from the competent authority of the federal German state. Fortunately, safety level 1 experiments only have to be recorded. Although approval of additional experiments of safety levels 2 and 3 should be given within 3 months, additional time is often needed when further information about the planned projects has to be forwarded to the competent authorities.

According to the Gene Law the use of GMOs such as, for example, live recombinant vaccines or gene therapy drugs for which marketing approval has already been obtained are not subject to Gene Law regulations. Moreover, medical treatment of human beings involving the use of genetically modified cells or viral vectors, which specify GMOs according to the Gene Law, is also not subjected to Gene Law regulations. This provision is interpreted to also extend to the treatment of human beings with gene therapy drugs such as non-viral vectors and other nucleic acids, although these drugs are not GMOs per definition of the Gene Law.

“the legal responsibility for the safety and quality of the drug produced rests with the entrepreneur”

Procedures regulated by the Gene Law not only include actual experimental work, but also the storage and the inactivation of GMOs. Thus, before marketing approval of gene therapy drugs has been obtained, patients would have to be treated within a registered gene laboratory with those gene therapy drugs which consist of or which contain GMOs like viral vectors or genetically modified cells. Details of such regulations have to await further decisions. It is to be expected that slightly different measures will be implemented by the competent authorities in each federal German state [25,29]. In summary, Gene Law regulations will ensure that necessary precautions are taken during the use of viral vectors and genetically modified cells to ensure the safety of human beings other than the patient and the environment.

Manufacture of gene therapy drugs

Gene therapy drugs have to be manufactured according to the necessary quality standards. If the company or the laboratory producing the drug commercially or professionally distributes it to others, a manufacturing authorization according to § 13 AMG ('Arzneimittelgesetz'; Drug Law) has to be obtained from the competent authority of the federal German state where the production facility is located (see Table 1). If the gene therapeutic is a vaccine or a blood product, the decision on granting manufacturing authorization is made under consultation of the Paul-Ehrlich-Institut. The German Directive termed 'Operation Ordinance for Pharmaceutical Entrepreneurs' ('Betriebsverordnung für pharmazeutische Unternehmer') should be used, if it is later intended to apply for marketing authorization. It is thus ensured that a quality control system including standard operating procedures (SOPs) is implemented and that the drugs are produced in facilities which comply with good manufacturing practice (GMP). However, approval is not only given for the production facility, but also for a particular drug and form of a drug, not a specific operation procedure. According to the Drug Law the competent authority may review detailed outlines of the production procedure prior to or after giving approval, inspect facilities or take samples for further analysis. It may also stop the manufacture. However, the legal responsibility for the safety and quality of the drug

produced rests with the entrepreneur. General guidance for the manufacture of gene therapy drugs can be taken from the European Note for Guidance 'Gene Therapy Products—Quality Aspects in the Production of Vectors and Genetically Modified Somatic Cells' and other guidelines listed in Tables 1 and 2.

If the physician, who will treat one or more patients with a specific drug, prepares or manufactures this drug himself, there is no legal obligation for approval of the production by the competent authority. In this case, production should follow the known and current standards of science and medicine. However, as the competent authority has to be notified according to § 67 AMG, it is also in charge of supervising the production facility.

Clinical trial or compassionate use

Since 1994 gene therapy drugs have been tested in Germany in clinical trials (phase I/II or III) or they have been used during compassionate use regimens [1,4,12,25,29–32]. Additional requests from mortally ill patients or, vicariously, their relatives for treatment with gene therapy drugs were placed. As non-registered gene therapy drugs are not easily produced or available, these and future requests will probably lead to the evaluation of these patients for admission to on-going or planned clinical trials.

A clinical trial is defined as a systematic study of medicinal products in human subjects, who may be patients or non-patient volunteers, undertaken in order to discover or verify the effects of and/or identify adverse reactions to investigational products, and/or to study their absorption, distribution, metabolism and excretion in order to ascertain the efficacy and safety of the products. Thus, according to a general definition the intention of a clinical trial is the gain of scientific knowledge unattainable from single cases. In contrast, compassionate use of medicinal products aims at helping single patients, e.g. by use of a novel drug. Neither forms of medical treatment of humans need any form of approval from competent authorities in Germany comparable with approvals of 'Investigational New Drug Applications' (INDs) or physician-sponsored INDs given by the Food and Drug Administration (FDA) in the USA. As described for the manufacture of drugs, there is a multitude of laws, directives and guidelines applicable to different aspects of a clinical trial. Clinical trials are regulated by the German Drug Law in order to provide protection for enrolled patients. The physician himself is responsible for the com-

passionate use of new drugs within the framework of the penal laws and is bound to certain scientific and ethical standards according to the 'Declaration of Helsinki' and to the professional law [30].

According to § 40 of the Drug Law the competent authority has to be notified prior to the beginning of a clinical study. The outline of a clinical trial is laid down within a protocol. This protocol corresponding to the 'Prüfplan' should contain the scientific background of the trial planned, ethical considerations and a description of the quality and safety testing prior to the treatment of patients with the drug. It should contain relevant information that assures a conduct according to current and sufficiently proven scientific standards. The information described in the protocol should correspond to descriptions given in the German Directive 'Arzneimittelprüfrichtlinien', which is a Directive outlining for German Drug Agencies specific issues pertinent to the review of data supporting applications for marketing authorization of drugs [18]. However, it may also be considered as a guideline for protocols describing clinical trials of all gene therapy drugs, no matter whether they are undertaken in view of a later application for marketing authorization or not.

The protocol also has to be filed with the competent local ethics committee formed according to the law of the federal German state (see Table 1). Sometimes, a positive vote is only reached after additional oral or written information has been forwarded by the investigator. The local ethics committee may choose to involve the central 'Committee for Somatic Gene Therapy' formed under the auspices of the German Medical Association in their decisions (see below) [20].

The competent federal higher authority ('Bundesoberbehörde') in Germany, which is either the Paul-Ehrlich-Institut, Federal Institute for Sera and Vaccines in Langen, or the Federal Institute for Drugs and Medical Devices (BfArM) in Berlin, has to be notified prior to the beginning of a clinical trial by presenting documents including the pharmacological-toxicological data of the drug, the clinical protocol ('Prüfplan') including the names and affiliations of the investigator, the locations where the trial is going to take place and the vote of the competent local ethics committee formed according to the law of the federal German states. Forms for this presentation are available by Internet (<http://www.pei.de/inhalt1.htm> → service links → Vorlageblatt 'Klinische Prüfungen'). According to § 77 AMG, the Paul-Ehrlich-Institut is the competent Federal Drug Agency for those gene

Table 3. On-going or planned clinical trials using gene therapy drugs in Germany (September 1997)

Drug	Disease	Transfer vector/method	Approach	Number of trials
Autologous tumour vaccine	Malignomas haematopoietic s., mal. melanomas, renal, pancreatic tumours	Retroviral vector, particle bombardement, transfection	<i>Ex vivo/ in vivo</i>	10
Cell marking drug	CML, AML, multiple myelomas	Retroviral vector	<i>Ex vivo</i>	3
Tumour cell killing drug	Brain tumour, lung cancer	Adenoviral vector cells releasing retroviral vectors	<i>In vivo</i>	6
Anti-rheumatic drug	Rheumatoid arthritis	Retroviral vector	<i>Ex vivo</i>	1

therapy drugs which are vaccines or blood products, whereas the BfArM is the competent agency for all other gene therapy products. If there is no positive vote of the ethics committee presented, the competent Federal Drug Agency may stop the initiation of the trial within 60 days after notification, but only if there is strong reason to consider the trial to be ethically unacceptable.

The competent authority of the land may visit the clinic, review the conduct of the clinical trial and stop it, if there is evidence for scientifically or legally incorrect conduct. It has also the right to take samples for further analysis. This is implemented by § 64 and § 65 AMG.

Quality and safety of gene therapy drugs

Similar to other biological drugs the use of gene therapeutics comprises pharmacological and toxicological risks. More importantly, safety issues connected with the transfer of the nucleic acids or the vehicles or reagents used have to be taken into account. In addition, risks for untreated third party individuals may result from vector spread. As pointed out in European 'Notes for Guidance', the specific safety and quality requirements for a particular drug should be assessed on a case-by-case basis [5,6]. General advice concerning the manufacture and subsequent testing of the safety and quality of a gene therapy drug can be taken from the regulations, directives and guidelines listed in Tables 1 and 2.

'Commission for Somatic Gene Therapy' of the German Medical Association

Following the publication of directives for somatic gene therapy ('Gentherapierichtlinien') by the Ger-

man Medical Association ('Bundesärztekammer'), a central advisory board termed 'Commission for Somatic Gene Therapy' was formed [20]. Publication of the directives by the German Medical Association was intended to define under the professional law of the medical society ethical standards that would also improve the safety and quality of the gene therapy drugs used in patients. The directives state that the competent local ethics committee advising the investigators of clinical trials should seek advice from the central committee as its members are selected experts in gene therapy. The vote of the 'Commission for Somatic Gene Therapy' may then be taken into account by the local ethics committee, when it comes to its appraisal.

Currently on-going or planned gene therapy trials in Germany

The first two gene therapy treatments were performed in Germany in 1994. Two groups at the University Clinics in Freiburg/Breisgau and Berlin announced almost on the same day that patients were being treated using autologous tumour vaccines. In Berlin T-lymphocytes taken from a renal cancer patient suffering from metastases were transfected *ex vivo* with a construct expressing the human IL-7 gene. The transfected cells were re-infused as an autologous cancer immuno-therapeutic. In Freiburg, human fibroblasts were transduced with an IL-2 gene construct and used in a mixture with autologous tumour cells for the treatment of patients suffering from carcinomas. Further gene therapy trials were subsequently undertaken and others are planned as listed in Table 3.

It is noteworthy that the majority of the gene therapy trials that have been performed in

Germany until today involved autologous tumour vaccines prepared by retroviral transduction. Autologous tumour vaccines do not need any marketing authorization because they are not finished medicinal products. Of course, those drugs could be commercially prepared from the cells taken from single patients. However, this would be a costly procedure rather unlikely to be followed. It is more likely that genetically modified allogeneic cells secreting one or more cytokines will be used in a mixture with autologous tumour cells. In contrast, retroviral packaging cell lines releasing vectors which contain suicide genes like those encompassing the coding region of the thymidin kinase gene of Herpes simplex virus (HSV-*tk*) are true finished drugs. They will also have to be licensed following the procedure defined by Council Regulation (EEC) No. 2309/93.

REGULATIONS IN THE UK

The UK government established in November 1993 the Gene Therapy Advisory Committee (GTAC) which replaced the former Committee on the Ethics of Gene Therapy (CEGT) for review of the protocols for gene therapy in the UK. The following tasks of the GTAC are listed: review of the clinical protocols for gene therapy research with respect to the scientific merit and the potential benefits and risks; cooperation with other agencies which have responsibilities in this field including local ethics committees and agencies with statutory responsibilities, i.e. the Medicines Control Agency, the Health and Safety Executive and the Department of the Environment; and advice of the UK Health Ministers on trends and development in gene therapy research. A case-by-case review is performed by the GTAC and approval of the protocol must be obtained before starting the clinical trial. The final statement of GTAC is always transmitted to the local research ethics committees and to the applicant.

Any clinical study must be referred to and gain the approval of a Local Research Ethics Committee (LREC) as it is also required for other clinical trials.

The licensing authority in the UK, the Medicines Control Agency (MCA), operates the national scheme for clinical trial certificates under the provision of the Medicines Act 1969. Before testing in patients the investigators have to apply to the MCA for a certificate of exemption (CTX).

REGULATIONS IN FRANCE

The National Advisory Committee on Ethics (CCNE) is an independent advisory body, created in 1982, which has no further legislative function. This committee can be referred to by the government, the National Assembly, any foundation or association or any individual. The CCNE may also decide to release comments or questions on any subject of its choice.

The 'Commission de Genie Genetique' (CGG) and the 'Commission de Genie Biomoleculaire' (CGBM) are in charge of regulations dealing with national implementation of EEC Directives on 'Controlled Use of Genetically Modified Microorganisms'. CGG and CGBM are directly connected to the French Ministry of University-Education and Research and the French Ministry of Environment, CGBM is additionally reporting to the French Ministry of Agriculture. The review of the clinical trials protocols is performed on a case-by-case basis by CGG and CGBM, approval is required before gene therapy is conducted in human subjects.

Local Research Ethics Committees 'Comité Consultatif de Protection des Personnes se prêtant à des Recherches Biologiques' (CCPPRB) are dealing with the protection of human beings which participate in biomedical research. Any protocols involving patients have to gain the approval of a Local Research Ethics Committee, as it is required for any other clinical trial.

Within the national medicines control agency, the 'Agence du Médicament', the Commission of Viral Safety has been installed which is directly connected to the French Minister of Health and which is dealing with questions on viral security like viral validation or safety aspects of the cell lines.

OBTAINING MARKETING AUTHORIZATION FOR GENE THERAPY DRUGS IN EUROPEAN MEMBER STATES

Marketing authorization for gene therapy drugs is obtained through the centralized procedure defined by Council Regulation (EEC) No. 2309/93. Data supporting marketing authorization can be included in a single file and forwarded to the European Agency for the Evaluation of Medicinal Products (EMEA). The Committee for Proprietary Medicinal Products (CPMP) appoints a rapporteur and a co-rapporteur from its members. The

rapporteurs appointed will prepare two independent assessment reports based upon evaluations from selected experts and prepare a list of questions to be answered by the applicant necessary for further clarification. The data evaluated relate to the quality, safety and efficacy of the drug as well as to environmental risks. Following a scientific discussion of the reports prepared and the applicant's response to the list of questions, the CPMP forwards its recommendation concerning the licensing of a drug to the Commission of the European Communities. This has to be done within 210 days after the file has been received. Within the following 90 days the Commission will come to a decision which is then published in the *Official Journal of the European Community*. In order to achieve short review times and a successful application, companies may choose to involve potential rapporteurs or experts in early discussions about the design of clinical trials and other relevant matters.

At present the German CPMP members are recruited from the Paul-Ehrlich-Institut (PEI) in Langen and the Federal Institute for Drugs and Medical Devices (BfArM) in Berlin. Both institutes are the Federal Drug Agencies in Germany which grant marketing authorization for drugs and certain diagnostics with the exception of those drugs regulated by Directive No. (EEC) 2309/93. In the process of obtaining marketing authorization for gene therapy drugs by the Commission of the European Communities, via the EMEA, the CPMP members of the Paul-Ehrlich-Institut or the BfArM may serve as rapporteurs during the evaluation of the dossier supporting the application. Applicants can propose to the EMEA suitable rapporteurs for the evaluation of their applications. The Paul-Ehrlich-Institut was proposed by the 'German Working Group on Gene Therapy' ('Deutsche Arbeitsgemeinschaft für Genterapie') as the federal higher authority competent for gene therapy drugs in Germany. Thus a number of sponsors of clinical trials, investigators or manufacturers of gene therapy drugs have already been seeking advice from the Paul-Ehrlich-Institut on the planning of clinical trials, the testing of the safety and quality of gene therapy drugs or other problems concerning their future marketing authorization.

There is also a new process coordinated by the EMEA which may help to reduce the time needed to bring a gene therapy drug to the European market which is called 'scientific advice'. Investigators or sponsors may submit a description of the issue which they seek advice on and ask precise questions. These are first evaluated by the EMEA

in order to avoid decisions on trivial issues that can be solved by consulting e.g. 'The Rules Concerning Medicinal Products in the European Community'. Reasonable questions are then evaluated by a group of experts chosen by the coordinators of the specific scientific advice. A hearing with members of the party seeking advice and the coordinator's group of experts as well as interested CPMP members is then adjourned in order to discuss the issues surrounding the questions submitted. A dossier containing the answers of the EMEA is subsequently discussed in the CPMP, and, if reviewed positively, forwarded to the sponsor or investigator, who submitted the questions. This process may help to solve pertinent problems prior to the beginning of or during the clinical trials.

OPINION IN GERMANY IS FAVOURABLE FOR GENE THERAPY DRUGS

Contrary to the view often expressed abroad, the public attitude towards gene therapy in Germany is currently favourable. Many hopes have been raised and the public is following the current developments in expectation of novel gene therapy drugs that will provide improved therapies for those suffering from ailments like cancer, AIDS or monogenic disorders. It is foreseeable that serious adverse events like the inadvertent infection of a patient with a replication competent virus as a result of the treatment with a gene therapy drug would seriously harm the development of gene therapy in Germany and probably worldwide. It is, therefore, the foremost obligation of the medical profession and the drug administrators as well as of politicians to promote gene therapy and to ensure the safe use of the gene therapy drugs.

The German working group on gene therapy ('Deutsche Arbeitsgemeinschaft Genterapie') was formed to promote the development of gene therapy and encourage clinical trials with such drugs as well as to provide a forum of discussion about possible regulatory problems in Germany. Independently, the German Medical Association published the already mentioned 'Guidelines for Gene Therapy' and formed under its auspices the 'Commission for Somatic Gene Therapy' in order to provide with expert assistance the local ethics committees which, in conjunction with the competent authorities of the 'Bundesländer' executing the Drug Law, are the main institutions advising investigators on the ethical aspects of clinical trials and also on quality and safety aspects of the drugs

used. Already in 1993, a working group ('Bund/Länder-Arbeitsgemeinschaft Genterapie') initiated by the German Ministry of Health (Bundesministerium für Gesundheit) was formed to evaluate the scientific background of gene therapy, the ethics of the treatment of humans using gene therapy and the legal framework in Germany. Following public and scientific discussions about gene therapy regulations, there seems to be a certain agreement that the German Drug Law provides sufficient protection for patients. Therefore, a special law regulating gene therapy in Germany is currently not planned to be developed. However, the early initiative of the German Medical Association to publish guidelines on gene therapy may have to be followed by a revision and the establishment of a more formal procedure to review gene therapy protocols. There are also voices raised expressing that the regulatory format of the 'Investigational New Drug Application' (IND) and the 'physician sponsored IND' known from the USA should be mirrored by equivalent procedures in Germany in order to provide early guidance for investigators planning clinical gene therapy trials and for companies aiming at obtaining marketing authorization for their gene therapy drugs.

In summary, initiation of clinical studies using gene therapy drugs can effectively be done in Germany. The laboratories where GMO containing material will be used or stored will have to be licensed as a gene laboratory following the requirements of the Gene Law. Once, the necessary pre-clinical data on the quality and safety of the gene therapy drug manufactured have been collected, there are the legal requirements of the Drug Law applying to clinical studies to be followed. The time needed for obtaining approval of the gene laboratory and the operations to be carried out and for obtaining a positive vote from the local ethics committee should not exceed 3–6 months.

The practical experiences in view of approvals of gene therapy protocols through ethic committees (local and German Medical Association in Germany) are very good. The discussion of clinical protocols is open to new forms of treatment as gene therapy certainly is. Proposals of clinical protocols in the gene therapy field which are according to the standards and which are based on solid pre-clinical data are discussed in a very constructive way. This demonstrates that there is a high interest in Germany for innovative treatments. The same experience was made in the UK. This attitude certainly also reflects the opinion of the physicians working in the experimental fields of

medicine or in indication fields in which present treatment regimens are relatively insufficient and unmet medical need is predominant. In addition, this positive atmosphere towards innovative pharmaceutical development also supports interests of the pharmaceutical industry already in this early and exploratory phase of a technology.

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