PERSEUS

Partners in Regulatory and Safety Services

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Analysis of the applicability of the contained use legislation for clinical trials

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Executive Summary

Starting 1997 some Member States treated trials with genetically modified micro-organisms ("GMMs") in clinical settings as "deliberate release of GMOs for any other purpose than for placing on the market" (so-called part B) according to Directive 2001/18/EC. Yet other Member States have restricted notifications to topics like veterinary and/or agronomic applications. They considered the GMM clinical trials as contained use and thereby regulated by Directive 90/219/EEC as amended by Directive 98/81/EC. Even within a Member State different approaches seemed applicable to different types of clinical GMM trials.

Overall the EU is an important player in the development of GMO medicinal products, although almost 3 times more clinical trials are conducted in the USA. Furthermore the overall contribution of GMOS clinical trials is still very limited: information on 430 trials with gene therapy and/or GMOs was collected compared to 10514 being the cumulative number of clinical trials –with and without GMOs- reported by Member States since May 2004 in the official EudraCT clinical trial database.

Not all clinical trials are addressed in the same way, even within a country. Trials for veterinary medicines, trials for gene therapy and/or trials for other human medicinal use can be subject to very divergent legal requirements. As a consequence also the way GMO aspects are included in those regulatory provisions may differ significantly. The determining factor for deciding between contained use and deliberate release is the specific characteristic of the organism (biological distribution, survival, shedding) although some authorities indicate that the fact that a human patient is free to leave the hospital is in itself sufficient reason to consider the trial as a deliberate release. Most of the clinical trials have been and are considered as contained use, evaluating the hospital or animal housing setting as containment facility. So far 13% of the clinical trials have been conducted as deliberate release. However, gradually more authorities are convinced that certain trials require a deliberate release approach, so the relative importance may increase.

Although the GMO regulation is not designed to cover clinical trials *per se*, national Competent Authorities (CAs) have developed several ways to cover the GMO safety aspects during the review of the application. Based on individual country reviews, four types of approaches were identified:

- **Co-existence of regulatory systems for clinical trials and GMOs.**
- **Cross-referencing between regulations, authorities and permits.**
- **Unified application leading to different, independent authorisations.**
- **Unified application leading to a single authorisation, covering all requirements.**

From the evaluation it seems that there is no particular safety area that cannot be addressed by contained use respectively deliberate release.

Both aim at protecting the environment and human health and therefore require a risk assessment preceding the activity.

Overall the GMO requirements are seen as an additional burden on an area which is already heavily regulated and scrutinised. Contained use seems in this respect more appropriate as most facilities would have more general contained use coverage also for other phases of the activity (e.g. preparation, storage...).

Overall CAs welcomed the initiative by the European Commission to compile the different approaches and stressed the need for further harmonisation. Areas that need to be considered for harmonisation include:

- **Risk assessment methodology**
- **Classification of organisms**
- **Criteria for determining contained use or deliberate release**
- **Confidentiality**
- **Scope of definition**
- **Format of applications and data requirements**

This harmonisation is urgently needed as developers reach advanced phase clinical trials and multi-centre trials. Facing uncertainty and multiple, scattered indications will hinder progress in this field.

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Annexes

1. Introduction

Perseus BVBA (Perseus) has been contracted by the European Commission, DG Environment to perform an analysis of the applicability of the contained use legislation for clinical trials.

Starting 1997 some Member States treated trials with genetically modified micro-organisms ("GMMs") in clinical settings as "deliberate release of GMOs for any other purpose than for placing on the market" (so-called part B) according to Directive 2001/18/EC[1]. So far such (clinical) trials were notified in Belgium, Ireland, The Netherlands, Spain, Sweden and the United Kingdom.

Yet other Member States have restricted notifications to topics like veterinary and/or agronomic applications (e.g. France and Italy). They seem to consider the GMM clinical trials as contained use and thereby regulated by Directive 90/219/EEC[2] as amended by Directive 98/81/EC[3]. Finally even within a Member State different approaches seemed applicable to different types of clinical GMM trials: e.g. although the United Kingdom has notified a range of trials as deliberate releases, many more have been dealt with as contained use.

1.1 A project performed for the European Commission

In a 2005 call for tender the European Commission, the objectives of the project were described as:

1. To collect and prepare background information and data concerning clinical trials and the suitability of the legislation under which they are governed, namely;
   - the nature of clinical trials conducted in Member States and the type of GMMs administered;
   - the facilities under which clinical trials are conducted;
   - the legal basis/regulatory mechanism under which such trials have been and are being carried out and levels of containment;
   - inspection and control of such trials.

2. To undertake a detailed appraisal of the current legislation, namely Directive 90/219/EEC and Directive 2001/18/EC, in terms of the suitability and adequacy of their provisions to address the potential risks from clinical trials.

In addition, a list of tasks was presented as a means to meet the objectives of the contract:

1. The contractor shall approach the national competent authorities to determine and collate the number and nature of clinical trials conducted in Member States, including accession countries, under Directives 90/219/EEC, 90/220/EEC and 2001/18/EC. This information should include the types of GMMs that have been administered, patient numbers, facilities where trials were performed (including containment), waste disposal, follow-up surveillance post patient discharge including survival, persistence and discharge of GMMs as well as inspection and control mechanisms.

2. The contractor shall identify and highlight the reasons for the choice of the specific legislation used to govern clinical trials in Member States

3. The contractor shall provide a critical overview as to whether the provisions of the governing legislation are deemed inappropriate or inadequate in terms of potential

[1] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106, 17/4/2001 P. 1 – 38)

[2] Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms (OJ L 117, 08/05/1990 P. 1 – 14)

[3] Council Directive 98/81/EC of 26 October 1998 amending Directive 90/219/EEC on the contained use of genetically modified micro-organisms (OJ L 330, 5/12/98 P.13 – 31)

risk control in line with their practical application and whether they may act as barriers to such trials.

4. The contractor shall identify additional legal provisions that may be required to address clinical trial activities to provide for a harmonised approach and the areas of clinical trials that are currently unclear and need further investigation.

5. Consideration of and information from clinical trials in third countries should be utilised and presented in the context of the above tasks.

Upon completion of the tender procedure the Service Contract was signed by the European Commission on November 30, 2005 with a fixed contract duration of 6 months from the date of signature. The methodology that was used is described in Annex 1 to this report. Data were collected via research (literature, internet...) and mostly via contacts with authorities.

All 25 Member States were contacted, including either the CA for contained use, deliberate release or for clinical trials. In addition contacts in Norway, Iceland, Switzerland and Liechtenstein were included. A complete list of all contacted people is provided in Annex 2.
Visits were scheduled in Belgium, the Netherlands, United Kingdom, and France. Other visits (Sweden, Germany and Italy) were explored but given the detailed interaction with the authorities deemed no longer necessary. For all cases where meetings and visits were not possible, phone interviews were conducted.

During the project Perseus was informed of two other initiatives, a 2005 inquiry by EMEA and a regulatory effort by the Euregenethy network that covered similar aspects. As much as possible it was tried to integrate the available information and avoid duplication.

1.2 Scope

1.2.1. Medicinal products consisting of or containing a GMO

Directive 2001/83/EC[4] provides a definition for a medicinal product as:

"Any substance or combination of substances presented for treating or preventing disease in human beings.

Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product."

In this definition "Substance" has to be very broadly interpreted as any matter irrespective of origin which may be:
- human, e.g. human blood and human blood products,
- animal, e.g. micro-organisms, whole animals, parts of organs,
- animal secretions, toxins, extracts, blood products,
- vegetable, e.g. micro-organisms, plants, parts of plants, vegetable,
- secretions, extracts,
- chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.

Specific groups of medicinal products are further defined. For instances medicinal product such as vaccines, toxins, serums or allergen products are referred to as immunological medicinal products, and for each category general and specific data requirements are identified.

[4] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28/11/01 P. 67 - 128)

The definition for a veterinary medicinal product is similar, replacing "human beings" with "animals".

1.2.2. Gene therapy products

The amendment of Directive 2001/83[5] in 2003 indicates advanced therapy medicinal products as based on manufacturing processes focussed on various gene transfer produced bio-molecules, and/or biologically advanced therapeutic modified cells as active substances or part of active substances.

In the amended Annex 1, PART IV ADVANCED THERAPY MEDICINAL PRODUCTS; a gene therapy medicinal product is defined as a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either *in vivo* or *ex vivo*, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression *in vivo*. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell.

In order to identify the product (substance), different cases are reviewed.

Gene therapy medicinal products based on allogeneic or xenogeneic cells
The vector is ready-prepared and stored before its transfer into the host cells. The cells have been obtained previously and may be processed as a cell bank (bank collection or bank established from procurement of primary cells) with a limited viability.

The cells genetically modified by the vector represent an active substance. Additional steps may be carried out in order to obtain the finished product. By essence, such a medicinal product is intended to be administered to a certain number of patients.

Gene therapy medicinal products using autologous human cells
The active substance is a batch of ready-prepared vector stored before its transfer into the autologous cells.
Additional steps may be carried out in order to obtain the finished medicinal product. Those products are prepared from cells obtained from an individual patient. The cells are then genetically modified using a ready-prepared vector containing the appropriate gene that has been prepared in advance and that constitutes the active substance. The preparation is re-injected into the patient and is by definition intended to a single patient. The whole manufacturing process from the collection of the cells from the patient up to the re-injection to the patient shall be considered as one intervention.

Administration of ready-prepared vectors with inserted (prophylactic, diagnostic or therapeutic) genetic material
The active substance is a batch of ready-prepared vector.
Additional steps may be carried out in order to obtain the finished medicinal product. This type of medicinal product is intended to be administered to several patients. Transfer of genetic material may be carried out by direct injection of the ready-prepared vector to the recipients.

1.2.3. Clinical trials

While clinical trials are repeatedly mentioned in legislation, there is no specific definition to determine the type of trial. Based on several indications one can describe a 'clinical trial' as an investigation of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy in human subjects (respectively animals) intended to:

[5] Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (OJ L 159, 27/6/03 P. 46 – 94)

- discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or
- identify any adverse reactions to one or more investigational medicinal product(s), and/or
- study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s);

In Directive 2001/82/EC[6] a distinction is made for veterinary medicinal products between Pre-clinical and clinical trials:

- Pre-clinical studies are required to establish the pharmacological activity and the tolerance of the product.
- The purposes of clinical trials are to demonstrate or substantiate the effect of the veterinary medicinal product after administration of the recommended dosage, to specify its indications and contra-indications according to species, age, breed and sex, its directions for use, any adverse reactions which it may have and its safety and tolerance under normal conditions of use.
- Unless justified, clinical trials shall be carried out with control animals (controlled clinical trials). The effect obtained should be compared with a placebo or with absence of treatment and/or with the effect of an authorised medicinal product known to be of therapeutic value. All the results obtained, whether positive or negative, shall be reported.

1.3 Inventory of trials

1.3.1. Information Sources

Several sources were verified in order to obtain an overview of the number and kind of clinical trials that have been conducted.

Some Member States have posted lists of contained use and/or deliberate release applications on the official websites. However, in many cases this information is not readily available, for instance it may be mentioned in a report of a Committee rather than in an overview. The level of detail is very varying. Whereas in some cases a summary of the application is available, in other cases the information is limited to a title of the project and an indication of the applicant. The main difficulty in comparing Member State data is the fact that no uniform reporting system is in place. In some cases the purpose of an activity may be indicated as “gene therapy”, but only refer to a laboratory experiment in preparation of an ulterior gene therapy application. In this review such uses were not included. Finally, during the interviews with CAs additional information was collected.

At the European level, the web site, managed by the Joint Research Centre of the European Commission on behalf of the Directorate General for the Environment publishes information regarding notifications about deliberate release trials and placing on the market of genetically modified organisms, as defined in Directive 2001/18/EC. In particular the section “Deliberate release into the environment of GMOs for any other purposes than placing on the market - Organisms other than plants[7]” is relevant for clinical trials that are handled as deliberate release. No European record of clinical trials performed as contained use is available.

Also the Clinical Trials Directive 2001/20/EC provides for the establishment of a European database of clinical trials, called EudraCT, serving as an overview of clinical trials being conducted in the community. This database is needed to facilitate communication on these clinical trials between the authorities, to enable each to undertake better the oversight of clinical trials and investigational medicinal product development, and to provide for enhanced protection of clinical trial subjects and patients

[6] Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to veterinary medicinal products (OJ L 311, 28/11/2001, p. 1 – 66)

[7] http://gmoinfo.jrc.it/gmo_browse_geninf.asp

receiving investigational medicinal products. The information that is required includes the fact that the product is and/or contains GMOs.

Access to the database is restricted to the competent authorities of the Member States, the Commission and the Agency. Sponsors submit electronic information to be included in the database to a Quarantine Area but do not have access to the database itself. The sponsor only has access to its own data.

With EudraCT being in full implementation, not all clinical trials are recorded yet. Based on the statistics of April 2006[8] there are 5855 clinical trial records included since May 2004. Given that a single trial record can cover trials in different Member States, the actual cumulative number reported by Member States is 10514. These overall indications provide a good comparison to understand the relative importance of clinical trials with GMOs.

As indicated above data access is restricted and the information could not be used for this project.

Finally, an interesting database is maintained by The Journal of Gene Medicine Clinical Trial and made available on the internet[9] . The information is searchable and is presented in charts and tables showing the number of approved, ongoing or completed clinical trials worldwide. The Interactive Database contains detailed information on individual trials. The data were compiled and are regularly updated from official agency sources (RAC, GTAC etc.), the published literature, and presentations at conferences and from information provided by investigators or trial sponsors. Consequently, information on some trials is incomplete. In this project we have used this database to verify and complement the other sources of information.

1.3.2. Overview

The complete table of clinical trials with GMOs collected using the methodology described before is provided as Annex 3. It is pointed out again that the information is only indicative, as official, validated lists with standard information are very difficult to access. In order to provide an overview, summary information of “The Journal of Gene Medicine Clinical Trial” is compared with information collected in this project.

Figure 1 provides an overview per country of gene therapy trials. In total approx. 1150 trials have been recorded. 65% have been conducted in USA and nearly 25% in European countries.

For the European countries our data give a relative frequency as shown in Figure 2. There are differences in actual numbers between the two sources, partly related to the methodology that was used in collecting information. “The Journal of Gene Medicine Clinical Trial” database focuses on human gene therapy trials. In this survey all trials with GMOs on humans and animals were included. Also compared to official data from authorities there are sometimes remarkable differences. One reason could be that not all clinical trials are everywhere considered to be involving a GMO, e.g. when naked DNA or plasmids are used. For this overview these were included to give a total picture. Furthermore some trials may have been performed at a moment where GMO legislation was not yet implemented. Finally, there could be differences in recording methodology if multiple trial sites are involved.

Based on this overview is can be concluded that one third of a total of 429 trials has been carried out in the United Kingdom. The data for France are incomplete and probably low as information for 2005 was not available. Based on personal communication, it has been indicated that the actual number for France would be 65 trials.

[8] Doc. Ref. EMEA/126728/2006
[9] http://www.wiley.co.uk/genmed/clinical/

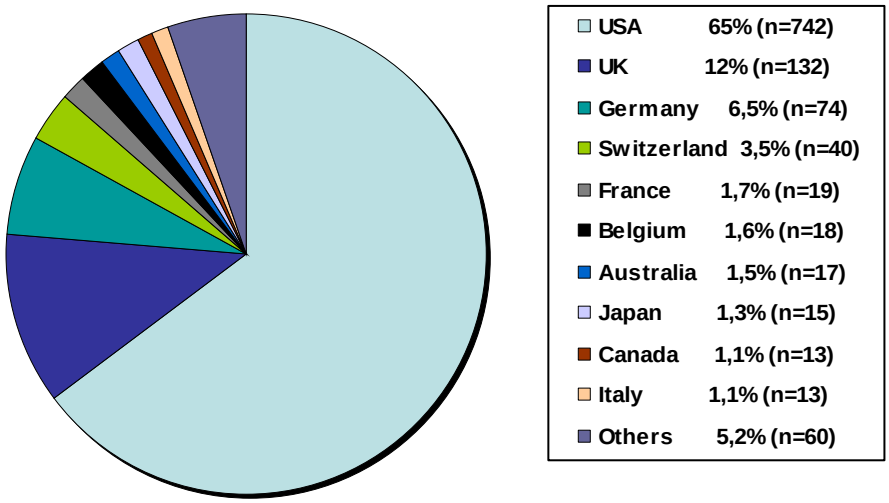

Figure 1 Relative contribution of number of gene therapy trials per country (information from "The Journal of Gene Medicine Clinical Trial" database).

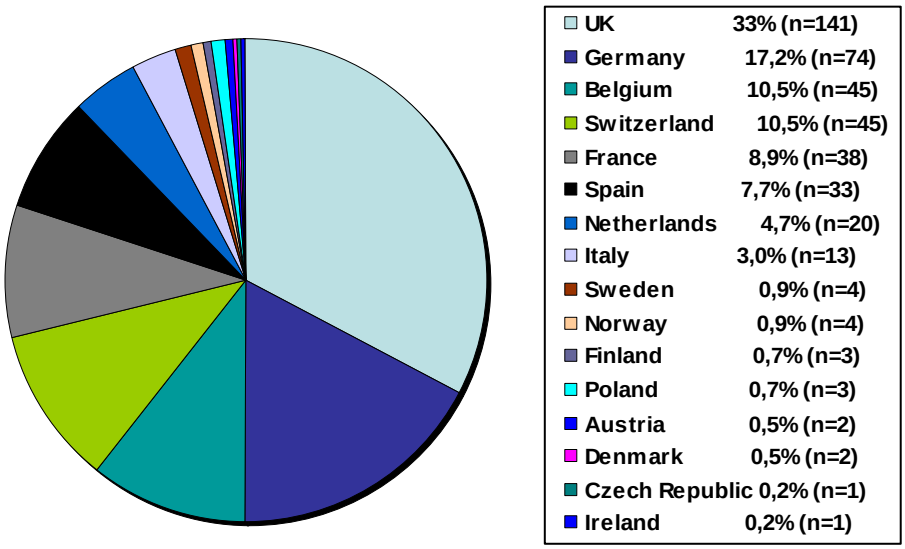

Figure 2 Relative contribution of number of gene therapy trials per country (information from Annex 3).

Most of the trials (67%) address some form of cancer (Figure 3), followed by a relative equal amount addressing monogeneic and vascular diseases.

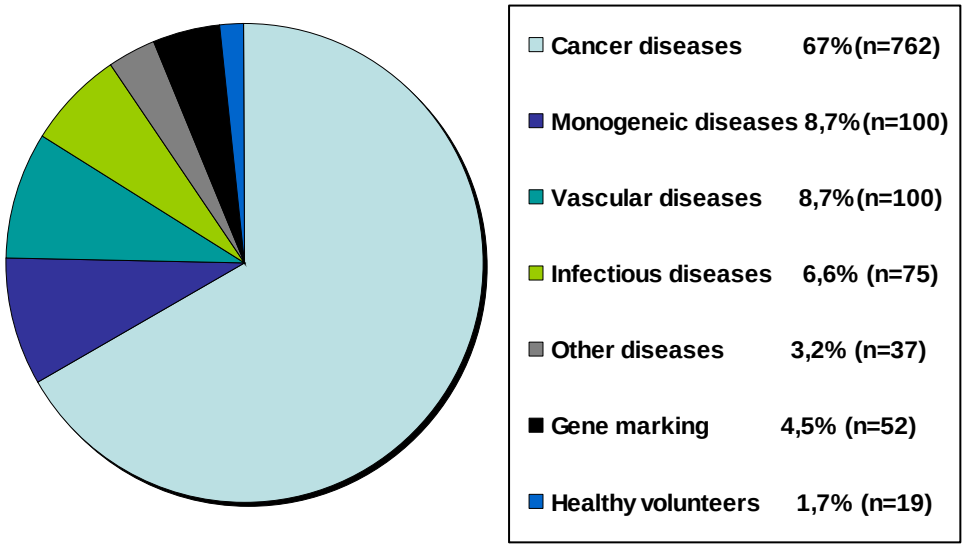

Figure 3 Relative contribution of global number of gene therapy trials per type of disease (information from "The Journal of Gene Medicine Clinical Trial" database).

Looking at the method of gene transfer adenovirus derived vectors are on top of the list both globally (Figure 4) and in the EU (Figure 5).

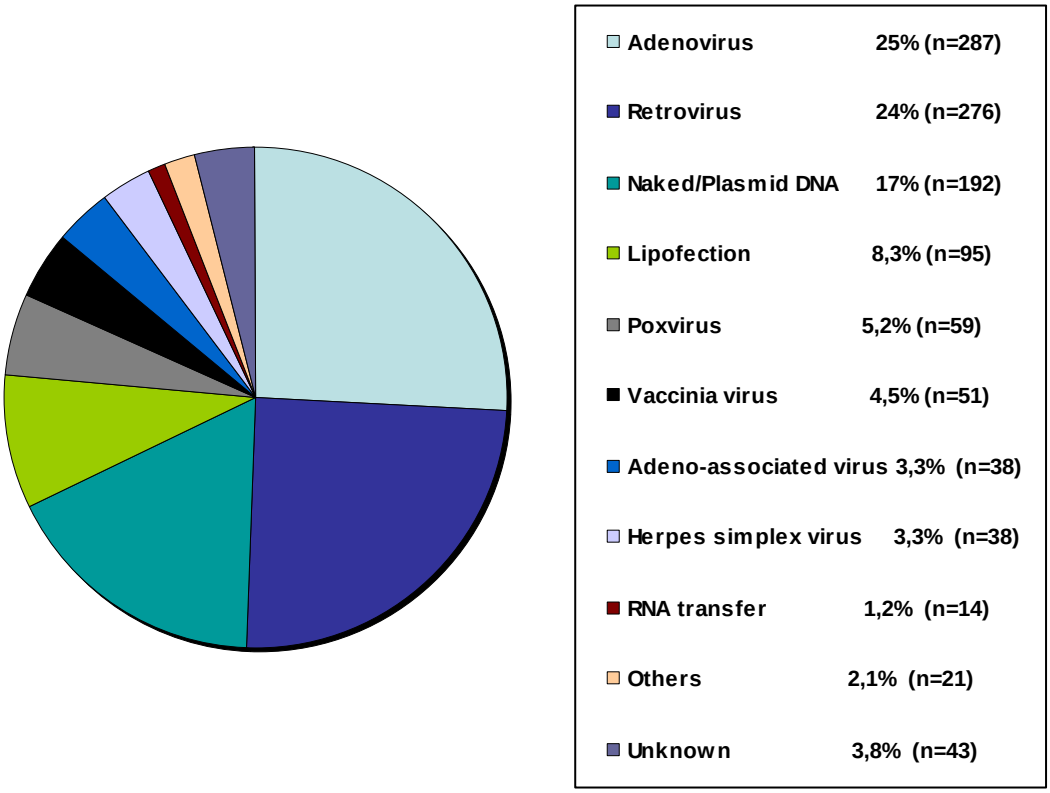

Figure 4 Relative contribution of global number of gene therapy trials per type of vector (information from "The Journal of Gene Medicine Clinical Trial" database).

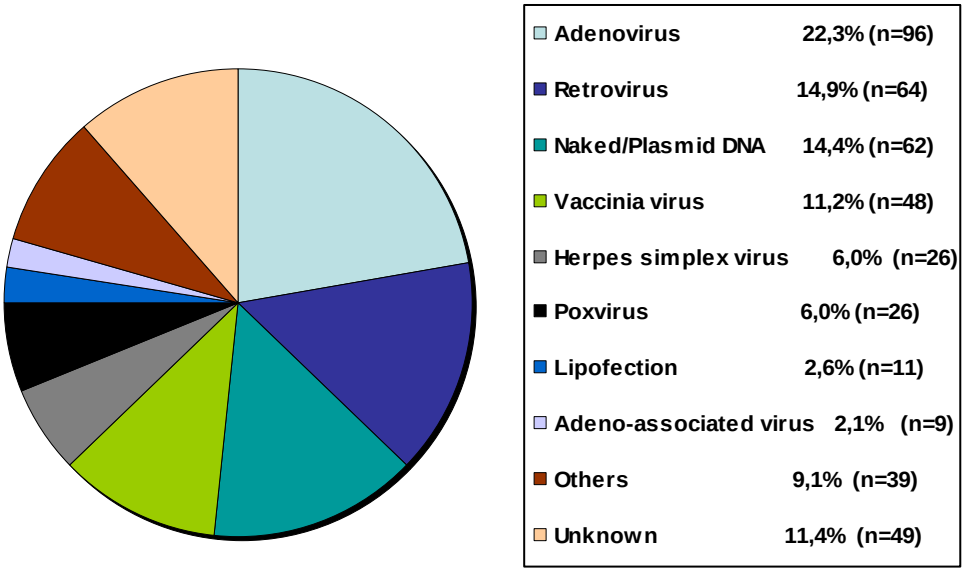

Figure 5 Relative contribution of number of gene therapy trials in the EU per type of vector (information from Annex 3).

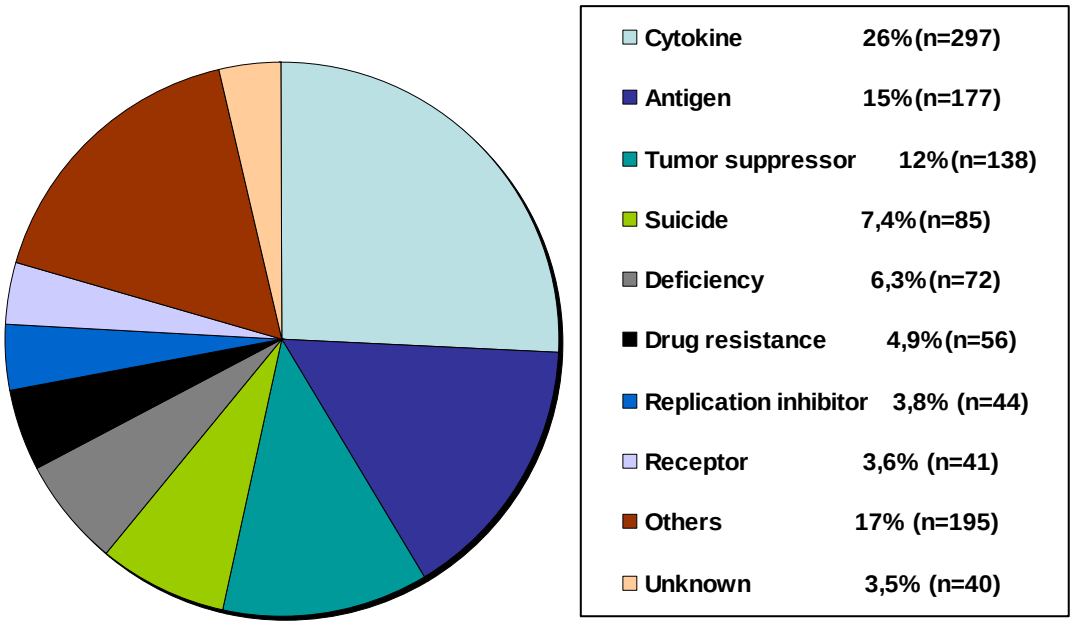

Figure 6 Relative contribution of global number of gene therapy trials per type of gene strategy (information from "The Journal of Gene Medicine Clinical Trial" database).

2. The European Regulatory Framework for Clinical Trials with GMOs

In this overview emphasis is given on those regulatory texts and practices that could have an effect on determining on the applicability of contained use versus deliberate release. It is not the intention to provide a full historical overview of different amendments, consolidations, etc. Rather the requirements as they prevail at the moment of the study are analysed.

2.1 GMO Regulation

In the EU, activities with GMOs, from creation to use, from storage to disposal, irrespective of the scale of the activity are covered by a so-called horizontal regulatory system. Irrespective of the type of product and its related product regulation, the GMO-specific regulatory framework was established to address risks and uncertainties that are the consequence of the special nature of the modified material.

Basically the GMO regulation provides 3 situations:

- Contained use (either for research, development or commercial production purpose),
- Deliberate release in the environment for placing on the market,
- Deliberate release for any other purpose (thereby including research and development activities).

Given the subject of this project, clinical trials are not considered to be a placing on the market. Therefore the analysis focuses on contained use and deliberate release for any other purpose than placing on the market.

While for certain cases the distinction between contained use and deliberate release is clear-cut, for others, including some clinical trials with GMMs, there seems to be an intermediate area. Most likely it is impossible to clarify this area by changing the definition without embarking on very detailed descriptions. Yet any interpretation needs to take into account the boundaries determined in the governing Directives.

Whereas in the earlier versions physical barriers were emphasised, the recent versions of contained use and deliberate release refer to specific containment measures, which could have a broader implication.

2.1.1. Contained Use of GMOs

The definitions in the respective Directives are following a coherent approach.
In Council Directive 98/81/EC Art 2 (c) contained use is defined as

> *"contained use" shall mean any activity in which micro-organisms are genetically modified or in which such GMMs are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with the general population and the environment;*

In the 2000 guidance note for risk assessment[10] foreseen in Directive 90/219/EEC further insight is provided

> *"3.4.3. Culture conditions*
> *….In combination with physical culture conditions that act as containment measures, both biological and chemical measures that are employed to protect the work can also contribute significantly to the containment measures that may be required. Examples of biological containment could well be auxotrophic mutants that require specific growth factors to be supplied to grow. Examples of chemical containment measures could be disinfectant solutions maintained in drainage systems."*

[10] Commission Decision 2000/608/EC of 27 September 2000 concerning the guidance notes for risk assessment outlined in Annex III of Directive 90/219/EEC on the contained use of genetically modified micro-organisms (OJ L 258, 12/10/00 P. 43 – 48)

"3.4.3.1. Environment likely to be exposed
The environment likely to be exposed will in most cases probably be limited to the workplace environment and the area immediately surrounding the facility, but depending on the specific characteristics of the contained use and the facility, a wider environment may need to be considered. The extent of the environmental exposure may be influenced by the nature and scale of the activity, but consideration should also be given to all possible modes of transmission into the wider environment. These can include physical modes (such as local drains, watercourses, waste disposal, air movement) and biological vectors (such as movement of infected animals and insects)."

2.1.2. Deliberate Release of GMOs

Art2 (3) of Council Directive 90/220/EEC[11] defines deliberate release as

"'deliberate release' means any intentional introduction into the environment of a GMO or a combination of GMOs without provisions for containment such as physical barriers or a combination of physical barriers together with chemical and/or biological barriers used to limit their contact with the general population and the environment;"

and this is restated in Art 2 (3) of Council Directive 2001/18/EC

"deliberate release. means any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment;"

2.1.3. Sectoral Legislation

Article 5 of Directive 2001/18/EC provides that the provisions for the deliberate release of GMOs for any other purpose than for placing on the market do not apply to medicinal substances and compounds for human use consisting of, or containing, a GMO or combination of GMOs provided that their deliberate release for any purpose other than that of being placed on the market is authorised by Community legislation which provides:

(a) for a specific environmental risk assessment;
(b) for explicit consent prior to release;
(c) for a monitoring plan;
(d) in an appropriate manner for requirements relating to treatment of new items of information, information to the public, information on the results of releases, and exchanges of information.

However, none of the relevant Community legislation covers the research and development phase, all focusing on the placing on the market. As a consequence all such deliberate releases are still subject to Directive 2001/18/EC articles 6 to 11.

The situation is quite different when it comes to placing on the market of GMOs as or in products Article 12 of Directive 2001/18/EC provides several cases where the provisions of art. 13 to 24 of the Directive do not apply. In particular §2 refers to medicinal products for human and veterinary use authorised by the relevant Community regulation, provided that a specific environmental risk assessment is carried out in accordance with the principles set out in Annex II to this Directive and on the basis of the type of information specified in Annex III to this Directive without prejudice to other relevant requirements as regards risk assessment, risk management, labelling, monitoring as appropriate, information to the public and safeguard clause provided by Community legislation concerning medicinal products for human and veterinary use.

[11] Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms (OJ L 117, 08/05/1990 P. 15 - 27)

2.1.4. Comparing contained use and deliberate release requirements

Rather than reviewing each legislative framework, it was attempted to compare the most relevant features of each approach in particular in relation to clinical trials. During the study the remark was made several times that neither of the Directives was really suited for handling clinical trials. In this initial theoretical analysis it was verified if there are any principal incompatibilities.

Table 1 Comparison of specific feature of contained use and "deliberate release" GMO legal framework.

	Contained Use	**Deliberate Release for purposes other than placing on the market.**
Reference to the Treaty establishing the European Community	Article 130s	Article 95
Purpose	To avoid adverse effects on human health and the environment which might arise from the contained use of GMMs.	To avoid adverse effects on human health and the environment which might arise from the deliberate release.
Scope	Genetically modified micro-organisms	Genetically modified organisms
Exclusion	GMMs approved for placing on the market	GMOs approved for placing on the market
	Possibility to exclude GMMs with established safety for human health and the environment	Possibly exclude medicinal substances and compounds for human use consisting of, or containing, a GMO or combination of GMOs provided that their deliberate release for any purpose other than that of being placed on the market is authorised by Community legislation which provides: (see sectoral legislation)
Scope of application	An application covers a type of activity with specified organism. It may cover several individual experiments over a longer period	Basically individual tests, although limited combinations can be presented in a single application
Containment	Specific containment measures are used to limit contact with, and to provide a high level of safety for, the general population and the environment	Intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment
Risk Assessment	Assessment of the contained uses as	An environmental risk assessment covering

	Contained Use	**Deliberate Release for purposes other than placing on the market.**
	regards the risks to human health and the environment they may incur	effects on human health or the environment
	Principles for risk assessment established	Guidance documents on risk assessment
	Assessment leads to risk classification (1, 2, 3 or 4)	Assessment leads to identification of risk factors and –if required- risk management.
	Periodical review of assessment and required to act upon new information	Need to act upon new information
	Procedures in case of accidental release	Procedures in case of unexpected findings
Safety measures	General principles and the appropriate containment and other protective measures as defined corresponding to the class of the contained use	No general principles in legal framework.
	Additional case-specific measures may be required	Risk assessments lead to case-specific measures; Conditions are specified in consent
	Conditions more fixed in time	Step-by-step approach should enable review of measures between individual trials
	Drawing up emergency plans where failure of the containment measures could lead to serious danger	Emergency response included in application
Procedure	Notification or approval procedure depending first or subsequent use and contained use class	Each application follows the same procedure
	Review period my be 0 days (notification contained use class 1 or subsequent class 2) up to 90 days (first use class 3 or 4)	Review period of 90 days. Possibility for a “differentiated” procedure (60 days)
	National or federal level decision	National level decision, but possibility of other Member Sate CAs to request application and raise concerns
	Formal approval only required in higher class contained use	Formal consent always required before activity may start

	Contained Use	Deliberate Release for purposes other than placing on the market.
		Post-trial reporting requirements
Exchange of information between Member State CA and Commission	Yearly summary report to the Commission on class 3 and class 4 contained uses	SNIF format circulated to Commission and other Member States Decision and grounds for decision communicated to Commission Yearly report of all GMOs released
Public information & consultation	Information available to the public at national level	Information to the public at national level and by the Commission
	Public consultation if authority decides appropriate	Public consultation always provided for

Both contained use and deliberate release aim to protect human health and the environment against a potential impact from an exposure to a GMO. Both require a risk assessment prior to the activity and these are based on a similar paradigm.

One might deduce that in contained use the emphasis is on infrastructure and containment thereby limiting exposure overall, whereas in deliberate release the impact and possible management of exposure is defined on a case-by-case basis. An important difference, which could affect clinical trials, is the risk classification for contained use. Depending on the risk class different procedures and measures are indicated. Since this initial evaluation is done by the applicant, it has been questioned if this would not lead to a large diversity in risk evaluations.

There are also difficulties in interpreting what containment measures entail. Is a product administered to a human being and which has been proven to remain with the body, contained? Or should the fact that a human with such administered product can freely walk around be considered as a deliberate release *de facto*?

Other practical differences between both regulatory approaches and important for clinical trials relate to:

- data requirements (felt to be more comprehensive for a deliberate release),
- length and complexity of procedure (more important for deliberate release),
- ease to repeat an activity (contained use more suited),
- evaluation of individual trials (deliberate release more suited, unless all activities belong to same risk class),
- public information (limited for contained use, major restrictions required for patient information).

2.2 Regulation for medicinal products and clinical trials

2.2.1. Regulation for medicinal products for human use

Directive 2001/83/EC[12] provided a consolidated Community code relating to medicinal products for human use. While it includes micro-organisms in the definition of possible medicinal substances, no particular indications are provided for dealing with GMMs. It describes in great detail the considerations for conducting clinical trials without reference to specific requirements for GMMs.

[12] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28/11/01 P. 67 - 128)

With the amendment of this Directive[13] in 2003, special reference is made to an environmental risk assessment for GMOs in "Part I - standardised marketing authorisation dossier requirements". Information pertaining to the environmental risk has to be presented in accordance with the provisions of Directive 2001/18/EC, taking into account any guidance documents published by the Commission in connection with the implementation of the said Directive.

In item 1.6. it is further stipulated that the information shall include:

- an introduction;
- a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC;
- the information requested in Annexes II to IV of the Directive 2001/18/EC, including detection and identification methods as well as unique code of the GMO, plus any additional information on the GMO or the product of relevance to evaluating the environmental risk;
- an environment risk assessment (ERA) report prepared on basis of the information specified in Annexes III and IV of Directive 2001/18/EC and in accordance with Annex II of Directive 2001/18/ EC;
- taking into account the above information and the ERA, a conclusion which proposes an appropriate risk management strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars which need to appear in the Summary of Product Characteristics, labelling and package leaflet;
- appropriate measures in order to inform the public.

The request for a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC suggests that the only reference that can be included when preparing for a placing on the market is a consent for a deliberate release.

Regulation (EC) N° 726/2004[14] provides further information on the procedure and requirements for the authorisation of medicinal products for human use. In the pre-amble (36) it is stated that:

> *"Environmental risks may arise from medicinal products containing or consisting of genetically modified organisms. It is thus necessary to subject such products to an environmental risk-assessment procedure similar to the procedure under Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms, to be conducted in parallel with the evaluation, under a single Community procedure, of the quality, safety and efficacy of the product concerned."*

For this discussion Art.6.2 is of particular relevance as it describes the information that shall accompany the application for a medicinal product for human use containing or consisting of genetically modified organisms. This includes:

- a copy of the competent authorities' written consent to the deliberate release into the environment of the genetically modified organisms for research and development purposes where provided for in Part B of Directive 2001/18/EC or in Part B of Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms (1);
- the complete technical dossier supplying the information required by Annexes III and IV to Directive 2001/18/EC;

[13] Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (OJ L 159, 27/6/03 P. 46 – 94)

[14] Regulation (EC) N° 726/2004 of the European Parliament and of the Council of 31 march 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30/4/04 P. 1 – 33)

- the environmental risk assessment in accordance with the principles set out in Annex II to Directive 2001/18/EC; and
- the results of any investigations performed for the purposes of research or development.

In art 6.3 it is further indicated that in the case of a medicinal product for human use containing or consisting of genetically modified organisms, the opinion of the EMEA Committee shall respect the environmental safety requirements laid down by Directive 2001/18/EC. During the process of evaluating applications for marketing authorisations for medicinal products for human use containing or consisting of genetically modified organisms, the Rapporteur shall carry out necessary consultations of bodies that the Community or Member States have set up in accordance with Directive 2001/18/EC.

This procedure is further elaborated and EMEA is developing guidance documents for applicants:

- New Market Authorisation (MA) applications for medicinal products for human use are assessed by the Committee for Medicinal Products for Human Use (CHMP). The CHMP consists of experts identified by the Member States. Two Members are identified as respectively Rapporteur and Co-Rapporteur for each application. The Rapporteur, and when appropriate, Co-Rapporteur chooses amongst the experts included in the European experts list available at the EMEA, those who will form his/her/their assessment team. He/she/they notify his/her/their choice to the EMEA prior to the start of the procedure.
- The CHMP publishes a European Public Assessment Report (EPAR) for every centrally authorised product that is granted a marketing authorisation, setting out the scientific grounds for the Committee's opinion in favour of granting the authorisation, plus a 'summary of product characteristics' (SPC), labelling and packaging requirements for the product, and details of the procedural steps taken during the assessment process. EPARs are published on EMEA's website, and are generally available in all official languages of the EU.
- In case the application concerns a product consisting of or containing a GMO, the rapporteur has to carry out the necessary consultations of bodies set up in accordance with Directive 2001/18. While the Regulation requires certain key-information to be provided (including technical and scientific information, the ERA and results of R& D investigations), EMEA recommends to provide also product information, a monitoring plan (or justification for its omission), a SNIF document and bibliographic references. As such the required information is completely in line with what is required by Directive 2001/18/EC.
- Regulation EC n° 726/2004 describes the need to include in an application a copy of the CAs written consent to the deliberate release. In case all research and development phases were carried out as contained use, it is not possible to provide such consent. In these cases the application would still be considered complete and the requirement not applicable.
- In practice, whenever such application is received at EMEA, the CAs for GMO of all Member States are informed and obtain an indication on the expected timeline for comments.
- The CHMP Rapporteur for the application will include in the assessment team an appropriately qualified assessor for the GMO data. The options include an expert connected with a research institution, an expert connected with a Directive 2001/18/EC Article 4.4 CA, such as the lead consulted Directive 2001/18/EC CA mentioned in the next paragraph, or an MA application assessor from a medicinal product agency, who may possibly be also involved with the assessment of other parts of the dossier.
- To expedite the progress of the consultation with those bodies established by the European Commission under Directive 2001/18/EC, and with the national GMO CAs designated by the member states for the purpose of implementing the Directive, the CHMP Rapporteur for the MA application may consider appointing one of the latter category to act as lead consulted CA. This lead consulted CA would act as the Rapporteur's contact point in the consultation, and would liaise as necessary with its

fellow GMO CAs on the review/assessment of the Module 1.6.2 documentation forwarded to it by the rapporteur.

- Whenever the lead GMO CA has completed its report, it is also provided to all other Member States, allowing for additional comments.
- In order to ensure completeness and coherence, an EMEA guideline is being developed. Two CHMP working parties provide guidance on issues with GMOs: the Biologics Working Party (BWP) and the Gene Therapy Working Party (GTWP). The Gene Therapy Working Party (GTWP) provides recommendations to the CHMP on all matters relating directly or indirectly to gene therapy. The Biologics Working Party (BWP) was established to provide recommendations to the EMEA scientific committees on all matters relating directly or indirectly to quality and safety aspects relating to biological and biotechnological medicinal products. BWP is also developing together with representatives of the GMO CAs a guideline on "Environmental Risk Assessments for Medicinal Products containing, or consisting of, Genetically Modified Organisms (GMOs) (Module 1.6.2)" (CHMP released for consultation January 2005). This guideline develops the data requirements and the Environmental Risk Assessment as required under Directive 2001/18/EC.

2.2.2. Regulation for clinical trials on medicinal products for human use

Directive 2001/20/EC[15] establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products in particular relating to the implementation of good clinical practice. Its main purpose is to protect clinical trial subjects by establishing quality, safety and ethical criteria to be observed. In this evaluation on a case-by-case basis the Ethics Committees, either established at local level (i.e. in the facility conducting the trial) or at national level, have a key role in evaluating the different aspects and providing an opinion before the trial can start.

The Ethics Committee has a maximum of 60 days from the date of receipt of a valid application to give its reasoned opinion to the applicant and the competent authority in the Member State concerned. No extension to the 60-day period is permissible except in the case of trials involving medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms. In this case, an extension of a maximum of 30 days shall be permitted. For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee in accordance with the regulations and procedures of the Member States concerned. In the case of xenogenic cell therapy, there shall be no time limit to the authorisation period.

Before commencing any clinical trial, the sponsor is required to submit a valid request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial and the competent authority then indicates if there are grounds of non-acceptance. However, a formal written authorisation is required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms.

It is further specified that this authorisation shall be issued without prejudice to the application of Council Directives 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms and 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms.

[15] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1/5/2001, p. 34 – 44)

2.2.3. Regulation for medicinal products for veterinary use

Parallel to the medicinal products for human use, Directive 2001/82/EC[16] provides a consolidated Community code relating to veterinary medicinal products. The Directive was amended by Directive 2004/28/EC[17].

The amended Art. 9 indicates that no veterinary medicinal product may be administered to animals unless the marketing authorisation has been issued or unless the competent national authorities, following notification or authorisation, in accordance with the national rules in force have accepted the tests for one of the following purposes:

- pharmaceutical (physico-chemical, biological or microbiological) tests,
- safety tests and residue tests,
- pre-clinical and clinical trials,
- tests assessing the potential risks posed by the medicinal product for the environment. This impact shall be studied and consideration shall be given on a case-by-case basis to specific provisions seeking to limit it.

All other indications relate to the requirements for market authorisation, without further specification or reference to genetically modified organisms.

Regulation (EC) N° 726/2004[18], already referred to for medicinal products for human use, provides also further information on the procedure and requirements for the authorisation of veterinary medicinal products.

For this discussion Art.31.2 is of particular relevance as it describes the information that shall accompany the application for a medicinal product for human use containing or consisting of genetically modified organisms. This includes:

- a copy of the competent authorities' written consent to the deliberate release into the environment of the genetically modified organisms for research and development purposes where provided for in Part B of Directive 2001/18/EC or in Part B of Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms (1);
- the complete technical dossier supplying the information required by Annexes III and IV to Directive 2001/18/EC;
- the environmental risk assessment in accordance with the principles set out in Annex II to Directive 2001/18/EC; and
- the results of any investigations performed for the purposes of research or development.

In art 31.3 it is further indicated that in the case of a medicinal product for human use containing or consisting of genetically modified organisms, the opinion of the Committee for Medicinal Products for Veterinary Use (CVMP) shall respect the environmental safety requirements laid down by Directive 2001/18/EC. During the process of evaluating applications for marketing authorisations for medicinal products for human use containing or consisting of genetically modified organisms, necessary consultations shall be held by the Rapporteur with the bodies set up by the Community or the Member States in accordance with Directive 2001/18/EC.

The interaction has been further elaborated in EMEA Standard Operating Procedure “Standard Operating Procedure on GMOs - Article 28” Document no.: SOP-V- 4012. The SOP describes the actions to be taken by EMEA staff when applications for a veterinary GMO are considered:

[16] Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to veterinary medicinal products (OJ L 311, 28/11/2001, p. 1 – 66)

[17] Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products (OJ L 136, 30/4/2004 p.58 – 84)

[18] Regulation (EC) N° 726/2004 of the European Parliament and of the Council of 31 march 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30/4/04 P. 1 – 33)

Research and Development Phase

Where necessary (i.e. where a product contains or consists of organisms within the meaning of Article 2(1) of Directive 2001/18/EC), the EMEA will draw the company's attention to Directive 2001/18/EC and to Article 28(2) of Council Regulation (EEC) No 2309/93. This should be done every time a potential applicant first makes contact with the EMEA Secretariat at the beginning of or during its development programme.

The potential applicant should then keep the EMEA Secretariat informed of any discussions that it might have with the Competent Authorities set up by Directive 2001/18/EC.

(a) If, during such discussions, it is established that the product contains or consists of GMOs within the meaning of Article 2(1) and 2(2) of Directive 2001/18/EC, no further action is required with regard to the marketing authorisation application until the letter of intent to submit an application for the granting of Community marketing authorisation is sent to the EMEA. The EMEA will however remind potential applicants of their obligations in this context.

(b) If it is established that the product contains or consists of organisms within the meaning of Article 2(1) of Directive 2001/18/EC, but that they are not GMOs within the meaning of Article 2(2) of Directive 2001/18/EC, the EMEA, through its Scientific Committees, may confirm this position. If confirmation cannot be given, the EMEA will contact the bodies set up by the Community and Member States in accordance with Directive 2001/18/EC.

Evaluation Phase

In the case of a veterinary medicinal product containing or consisting of GMOs within the meaning of Article 2(1) and 2(2) of Directive 2001/18/EC, the application must be, in accordance with Article 28(2) of Council Regulation (EEC) No 2309/93, accompanied by:

• a copy of any written consent or consents of the Competent Authorities to the deliberate release into the environment of the GMO for research and development purposes, or for any other purpose than placing on the market where provided for in Part B of Directive 2001/18/EC;…

The responsibility to assess whether the release into the environment, for the purposes of research or development, poses a hazard or not rests with the Competent Authority set up by Directive 2001/18/EC in each Member State, where any investigations take place.

However, it is the responsibility of the EMEA, through its Committee for Veterinary Medicinal Products, to assess whether the placing on the market of a veterinary medicinal product containing or consisting of GMOs within the meaning of Article 2(1) and 2(2) of Directive 2001/18/EC, poses a hazard to human health and/or to the environment. Such an assessment is made in conjunction with the other particulars submitted for the granting of a Community Marketing Authorisation.

Once a pre-submission meeting has taken place and the CVMP has appointed a Rapporteur and Co-Rapporteur, the EMEA Secretariat will write to the Competent Authorities under 2001/18/EC to advise them that an application for a product falling under Article 28.4 of Council Regulation (EEC) 2309/93 is expected, with an indication of the intended date of submission. In practice regular faxed updates are provided to the Competent Authorities indicating the status of each product containing or consisting of a GMO, whether authorised, under evaluation or anticipated.

To expedite the progress of the consultation with the Competent Authorities under 2001/18/EC, the CVMP Rapporteur should consider appointing one of the Competent Authorities under 2001/18/EC to act a "lead consulted Competent Authority" (CA) to act as contact point in the consultation and who would liaise as necessary with fellow CAs on the review of Part IIH as provided by the Applicant.

The Secretariat will underline that the data provided by the Applicant and any other documentation are strictly confidential.

Finally, the CVMP has communicated a “GUIDELINE ON GMOS - UPDATED NOTICE TO APPLICANTS (NTA) GUIDANCE” (Doc. Ref. EMEA/CVMP/1151/04 – CONSULTATION). This guideline as well as any previous document included in “The Rules Governing Medicinal Products in the European Unions” only refers to the need to include Part B consents.

3. Member state review

Based on the interviews as well as on other sources of information a summary is provided on how a clinical trial with a GMO is handled in the respective Member State. Most cases relate to clinical trials with medicinal products for human use. Where possible a specification was provided if the treatment of gene therapy is different. Also in particular cases information is provided on how clinical trials for veterinary medicines are handled.

3.1 Austria

3.1.1. Clinical trials for human purposes

The Ministry of Health and Women (Bundesministerium für Gesundheit und Frauen, BMGF) is the Competent Authority for Clinical trials for human medicines.

Clinical trials for human medicines are included as a specific chapter in the Gene Technology Act (Gentechnikgesetz or GTG; BGBl. Nr. 510/1994 and amendments, BGBl. I Nr. 127/ 2005 being the most relevant[19]). As such clinical trials for gene therapy are considered a separate category in addition to contained use and deliberate release. The chapter is headed "Gene analysis and Human Gene Therapy" (IV. Abschnitt Genanalyse und Gentherapie am Menschen) and requires applicants to submit an application and obtain an explicit permit before starting the trial.

The 4th amendment (4. Änderung des Gentechnikgesetzes; BGBl. I Nr. 127/2005[20]) aimed at a state-of-the-art adapting of the law in the field of gene analysis and gene therapy.

The Pharmaceutical Product Act (Novelle zum Arzneimittelgesetzes; BGBl. I Nr. 35/2004[21]) regulates clinical trials in general (transposition of Directive 2001/20/EC) with specific reference to clinical trials with GMOs.

The decision is taken by the Ministry for Health and Women, based on both the Gene Technology Act and the Pharmaceutical Product Act. As a consequence the advice of two advisory bodies, the Advisory Board for Biotechnology (Gentechnikkommission) and the Pharmaceutical Advisory Board (Arzneimittelbeirat) is taken into account. The applicant has to submit two different applications (one due to the Arzneimittelgesetz and the other due to the Gentechnikgesetz), but will receive a single permit fulfilling all obligations.
There are guidance notes for applicants. Check lists for all necessary documents and guidelines are available at the BMGF website[22].

In evaluating the proposals, the main criterion is safety. There is much attention of qualification of staff, on appropriate and functional equipment and on protection of personal data.

Once a permit is delivered there are quite stringent reporting requirements (e.g. on any facts or circumstances that would endanger health or the environment, on changes in protocol, staff or equipment)

Some trials (less than 10) have been reviewed and approved. They have not triggered concerns of spreading GMOs beyond the clinical setting.

[19] http://www.bmgf.gv.at/cms/site/detail.htm?thema=CH0264&doc=CMS1085735125660)
[20] http://www.bmgf.gv.at/cms/site/attachments/5/2/0/CH0264/CMS1085735125660/gtg-nov._11-05.pdf
[21] http://ris1.bka.gv.at/authentic/index.aspx?page=doc&docnr=1
[22] http://www.bmgf.gv.at/cms/site/detail.htm?thema=CH0008&doc=CMS1083333414077.

3.1.2. Clinical trials for veterinary purposes

For veterinary purposes, the trials would be considered as a specific case of either contained use or deliberate release. The situation is more complex and requires also the interaction between authorities at national and regional level.

Different pieces of legislation are to be taken into account.

- For the GMO part this is the Gentechnikgesetz (GTG; BGBI nr 510/2005 and amendments).
- For the use of animals this is the Tierversuchsgesetz (TVG; BGBl. Nr. 501/1989, and amendments BGBl. I Nr.169/1999; BGBl. I Nr. 136/2001 and BGBl. I Nr. 162/2005) (transposition of Directive 86/609/EEC).

Clinical trials for veterinary purposes are judged on a case-by-case basis.
Depending on e.g. the risk of shedding in the environment and the possibility to avoid it, the trials will be conducted as contained use trials or as deliberate release.

Contained use:
Up to now all applications on animals were carried out under containment conditions (in accordance with Table 1C in Annex IV of 98/81/EC and the requirements of Dir 86/609/EEC).
In most cases it is understood that no GMMs are given off by the animal, e.g. transplants of GM bone marrow or pre-clinical trials for *ex vivo* gene therapy. Even in cases where shedding of GMMs from the animal is to be expected, e.g. testing of live GM vaccines, the whole animal plus GMM can be kept under the appropriate contained conditions according to Annex II of 98/81/EC.

Deliberate release:
Would be applicable if GMM shedding is expected and the animal is not (cannot be) kept in containment.

When the trials are to be performed in universities or the Austrian Academy of Sciences (residing under the Ministry of Education, Science and Culture) both applications are handled by the Ministry of Education, Science and Culture. Other notifiers have to apply to the Ministry of Health and Women in relation to the GMO aspect and to the regional authorities (9 Bundesländer) for the animal aspect.
For biosafety level 1 or 2 a notification (implicit consent) is necessary; for biosafety level 3 or 4 a notification + explicit consent is needed. To comply with the Tierversuchsgesetz a permit is needed (explicit consent).

No guidance notes have been issued yet, as there were very few applicants so far. Regional authorities who authorise animal experiments were informed about the double requirements for such applications.

Research projects with GMMs on animals as models for human diseases have been conducted; clinical trials for veterinary purposes in the strict sense (i.e. treating animal diseases) have not been performed. In research projects with animals, the animals (usually rodents) are kept in containment until they are euthanised and safely disposed of.

With regard to the Tierversuchsgesetz, the text of the law, application forms and guidelines are available on the website of the Ministry of Education, Science and Culture[23].

[23] http://www.bmbwk.gv.at/forschung/recht/tierversuche/tv_ueber.xml

3.1.3. Clinical trials: contained use vs. deliberate release

Austria	
Contained use:	In cases containment measures are in place
Deliberate release:	In case shedding is possible and/or the patient/animal cannot be kept in containment
Special Gene Therapy category	Trial with humans when in containment and dealing with genetic analysis and/or gene therapy.

3.2 Belgium

3.2.1. Legal framework

For R&D with GMO-medicinal products the Federal Public Service (FPS) Health, Food Chain Security and Environment; DG3 Protection of Public Health; Medicinal products (DGMP) is the competent authority. Proper reference is included in the Royal Decree[24] of 21 February 2005 implementing the deliberate release Directive.

When the activity is considered to be a contained use, then the relevant regional authorities are competent for that part. However, the FPS stays involved concerning the clinical trial procedure and permit.

The Division of Biosafety and Biotechnology (SBB) acts as technical adviser and as secretariat for the Biosafety Council. Irrespective of the procedure, proposals of gene therapy clinical protocols are reviewed by the ad hoc Expert group "Recombinant viral vectors, virosomes, recombinant vaccines, gene therapy" of the Belgian Biosafety Advisory Council or directly by the experts of the SBB as a function of the regulatory framework and of the degree of familiarity of the Biosafety Council with the proposed project.

Clinical research in gene therapy using genetically modified organisms (GMOs) and/or pathogen organisms falls under the scope of Belgian biosafety regulation. In all cases, an environmental risk assessment has to be performed and an authorisation must be obtained according to the Belgian regulations on contained use of GMOs and/or pathogen organisms which implement Directives 90/219/EEC and 98/81/EC, albeit to cover the handling and storage of the GMO before and during the trial, the procedure for administration of the product to the patients, the handling of biological samples and the disposal of waste. At the moment trials with naked DNA would be only subject to the clinical review.

In the case of multi-centre trials and/or for those trials that involve ambulatory medicine and the risk of excretion of GMOs by the patient into the environment, the Belgian regulation on the deliberate release of GMOs which implements Directive 2001/18/EC can/must also be applied.

As all interventional clinical trials for human medicine, clinical research in gene therapy using GMOs and/or pathogen organisms falls under the scope of the new Belgian law of 7 May 2004[25] experimentation on human beings implementing Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. In Belgium the legal scope of “clinical trials” has been expanded to include all experimentation on human beings.

A clinical trial in the field with a veterinary vaccine consisting of or containing a GMO falls under the scope of the Belgian regulation on the deliberate release of GMOs which implements Directive 2001/18/EC. Most veterinary clinical trials are performed in “real

[24] Royal Decree of 21 February 2005 regulating the deliberate release in the environment and placing on the market of genetically modified organisms and of products containing them.
[25] Law of 7 May 2004 concerning the experimentation on human beings.

case" situations (stables, field...) and are as a consequence considered deliberate release. In case the trial is conducted at the location of the developer under containment conditions, it might be a contained use.

As far as contained use is concerned, the authorisation(s) of the concerned region(s) is/are given for a defined operation in a given installation for several years (e.g. 5 years). An operation can not only cover a particular protocol but also a whole program of clinical trials. This program may integrate several protocols of the same kind (e.g. phase II and III protocols using one type of vector with one transgene 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 thereafter be allowed if there is no modification in the biosafety frame of the program. A deliberate release authorisation can cover a particular gene therapy clinical trial conducted in different sites.

3.2.2. Procedural aspects

In the case of a clinical trial requiring a deliberate release of GMO, the application is submitted to the Directorate-General Public Health Protection: Medicinal Products and is also sent to the SBB and the concerned regional Ministers. The dossier is reviewed by the Belgian Biosafety Advisory Council (BAC) which transmits its advice to the competent authority (DGMP) and the regional minister(s). Within 5 days after validation of the dossier, the FPS also has to foresee a public consultation period of 30 days. Within 10 days after termination of the public consultation, the FPS informs the Minister of Public Health and the concerned regional minister(s) regarding the received public comments and shares the comments related to biosafety with the BAC. Based on the BAC recommendations, the recommendations of the regional minister(s) (if any) and the public consultation, the DGMP submits a decision proposal to the Minister of Public Health or his delegate for final decision. This decision is delivered after maximum 90 days from the start of the procedure.

While in practice the procedure for human and veterinary products is very similar, they follow different legal provisions.
For a clinical trial on humans, the approval by the Minister or his delegate takes into account the opinion of the local ethics committee, the clinico-pharmaceutical evaluation made by the DGMP and the BAC's opinion on the GMO aspects. On the veterinary side, the approval by the FPS takes into account the opinion of the ethics committee of the Directorate General of Animal Health for preclinical trials (confined use). For the deliberate release no ethical approval is necessary.

3.2.3. Considerations

Some 20 human and 3 veterinary trials have been reviewed. Overall the requirements for a GMO clinical trial are felt to be very heavy, especially when compared to other applications for which there is no similar obligation.

Even if contained use is chosen, the potential impact of a release or a patient leaving the experimental setting is evaluated. In case that the risk would be unacceptable the trial would not be permitted. This is even the case for certain conditions that are deemed to be hard to control completely. E.g. when a vaccination of cats occurred, one of the conditions was to keep the animals at home for a certain period. In the risk assessment the possible impact of not all owners following this obligation was included. (Such conditions also pose difficulty for the applicant to comply, as the applicant cannot fully control the behaviour of the people/animals participating).

Belgium has already stressed the importance of a harmonisation at European level about the interpretation of contained use or deliberate release in the case of clinical trials involving humans.

3.2.4. Clinical trials: contained use vs. deliberate release

Belgium	
Contained use:	- All preparatory and subsequent activities - Veterinary trial conducted at location of developer under containment - Trials in containment with no risk for release
Deliberate release:	- Ambulatory medicine - Risk of excretion - Veterinary trial conducted under real-life situations.

3.3 Cyprus

3.3.1. Legal framework

contained use and deliberate release provisions are in place in Cyprus, so far essentially being focussed on agricultural products. Very limited experience has been gathered.

Overall there are very few clinical trials in Cyprus. This is partly related to the relatively small population. Given the small community it has been preferred to establish a central ethics committee. They would also be expected to evaluate applications for gene therapy. So far no such request has been made.

There are no particular provisions beyond what is contained in Directives 2001/20/EC and 2001/83/EC as far as GMOs are concerned.

3.3.2. Clinical trials: contained use vs. deliberate release

Cyprus	
Contained use:	Both are possible. No experience yet.
Deliberate release:	

3.4 Czech Republic

3.4.1. Relevant regulation

Clinical trials are generally regulated by the Czech Act No. 79/1997 Coll., on Pharmaceuticals, as amended. Specific conditions for trials with products containing GMOs are set in this Act. A reference is made to Act No. 78/2004 Coll. on genetically modified organisms and genetic products, indicating that an authorisation according to this act is required.

Act No. 79/1997 Coll., on Pharmaceuticals and Amendments to Some Related Acts (Consolidated text as implied by amendments laid down by Act No. 149/2000 Coll., Act No. 153/2000 Coll., Act No. 258/2000 Coll., Act No. 102/2001 Coll., Act No. 138/2002 Coll., Act No. 309/2002 Coll., Act No. 320/2002 Coll. and Act No. 129/2003 Coll. has been issued as the Act No. 269/2003 Coll. Coll. Volume 90 of 22.8.2003) is available at the authorities website[26]. Instructions for applicants concerning requirements of the Czech Ministry of the Environment ("Clinical trials on products containing genetically modified organisms") are also available[27].

Act 78/2004 on GMOs covers both contained use and deliberate release of GMOs.

[26] http://www.sukl.cz/en02/en0201.htm
[27] http://www.sukl.cz/en02/en0205.htm

Act No.78/2004 Coll. on the use of genetically modified organisms and genetic products and 209, DECREE of 15 April 2004 on detailed conditions for the use of genetically modified organisms and genetic products, are available at www.biosafety.cz
For the GMO aspect of clinical trials no guidance notes are written. Consultations are provided individually.

Clinical trials with GMOs are assessed on case-by-case basis, i.e. they can be considered as contained use or deliberate release depending on the conditions of the application and metabolism of the product.

The competent authorities are the State Institute for Drug Control[28] and the Ministry of the Environment of the Czech Republic[29].

Permits have to be applied for to both authorities. According to the Czech legislation, each subject has to be authorised for the use of GMOs that has not been approved for placing on the market. That means each hospital or medical institution and also the company organising the trial have to get the authorisation.

So far, one clinical trial is being carried out (with a recombinant adenovirus) and one notification is pending; both are with human medical products and are conducted as contained use.

At the Ministry of Environment problems were mentioned that are encountered in deciding whether regulations for contained use or for deliberate release apply, considering the specificities of the GMO and the risk assessment.
The administrative burden for contained use is not in proportion to the relatively short period for performing clinical trials.
Regulations, notification formats etc. for deliberate release are not adapted for clinical trials with pharmaceuticals.

3.4.2. Clinical trials: contained use vs. deliberate release

Czech Republic	
Contained use:	Both are possible depending on the conditions of the application (containment) and metabolism of the product.
Deliberate release:	

3.5 Denmark

3.5.1. Relevant regulation

The Danish Medicines Agency[30] evaluates both the quality of the investigation and the safety of the patient during the clinical trial[3132]. The scientific ethics committee, which evaluates the ethical aspects of the investigation, must also be notified of clinical trials. In order for a trial to be approved, both the scientific ethics committee and the Danish Medicines Agency must give their approval.

Patient trials with products containing living genetically modified organisms are subject to the Danish Environment and Gene Technology Act[33], more specifically this Act's rules on research. The rules are contained in the Danish Working Environment Authority's

[28] http://www.sukl.cz/enindex.htm
[29] http://www.env.cz/
[30] Danish Medicines Law
[31] Executive order on clinical trials on medicinal products, human use (2004)
[32] Guideline for applications for authorisation of clinical trials of medicinal products on humans, May 2005
[33] Act No. 356 of 6 June 1991 on the Environment and Genetic Engineering (Latest amended by Act No. 384 of 6 June 2002, Consolidated Act No. 981 of 3 December 2002)

(DWEA) Executive Order (No. 642 of 28 June 2001)[34] on "gene technology and working environment".

One of the things this Executive Order covers is the requirement for notification of the classification of premises at which all or part of the trial is to take place, as well as notification of projects. The purpose of the notifications is to safeguard both the working environment and the external environment. The DWEA will then grant authorisation of both the premises and the trial.

A cooperative agreement has been entered into by the Danish Working Environment Authority and the Danish Forest and Nature Agency on the evaluation of certain notifications of the classification of premises and notification of research projects.

Notifications on the classification of premises for gene therapy and notification of projects concerning the use of living, genetically modified micro-organisms for gene therapy are to be submitted to the Danish Working Environment Authority.

All clinical trial activities are initially considered as contained use. Any proposal is automatically copied to the Danish Forest and Nature Agency. They will review the file and provide additional comments, e.g. on the duration that patients are expected to be kept inside. In specific cases, e.g. when a risk for shedding is identified, they may decide that the trial application be handled as a deliberate release. So far this has not occurred yet.

Medicinal product trials with gene therapy must be notified to the Danish Working Environment Authority, cf. above. This may take place at the same time as the application to the Danish Medicines Agency. Both procedures run independently.

The "GMO" application is completely separate from the "clinical trial "application. Both follow the respective procedures as required for other GMO uses, respectively clinical trials. It is expected that when an application is presented to the Danish Medical Authority (DMA), that they point out that there are GMO requirements. This is for instance included in the guidance document provided by DMA. The clinical trial approval will state as a condition that an authorisation from the Danish Working Environment Authority needs to be in place.

While there is no procedural link between the procedures, the authorities meet 3 to 4 times per year to exchange on applications and on regulatory developments. If an application demands special care, then the different authorities will meet and discuss *ad hoc*. There is also an agreement to make joint inspections when needed.

In some borderline cases (e.g. naked DNA or killed viruses), applicants asked the opinion whether these would require a GMO approval. Such requests have been reviewed and were deemed to be outside of the scope of the GMO specific regulation. They would of course still require a clinical trial approval.

Whereas the DMA focuses on safety of the patient, the DWEA review will pay special attention to risk and uncertainty for the clinical trial staff, to waste treatment and handling of samples. It is very much a case-by-case exchange with the clinical team.

3.5.2. Clinical trials: contained use vs. deliberate release

Denmark	
Contained use:	Default contained use, but could be deliberate release depending on specifics of the case (intention of introduction and risk for release).
Deliberate release:	

[34] Statutory Order on Genetic Engineering and the Working Environment (No. 642 of 28 June 2001) (Issued by the Danish Working Environment Authority)

3.6 Estonia

3.6.1. Legal framework

Both the contained use and the deliberate release Directive have been implemented in national law[35], but so far neither deliberate release applications, nor clinical trials have been approved in Estonia.

The Competent Authorities for each of the areas have been identified: for deliberate release the Nature Protection Department (Min. of Environment) is the lead agency, for contained use Labour Inspection (Min. of Environment) is in charge and for food and feed aspects the Veterinary and Food Board (Min. of Agriculture) has been appointed.
There are no particular provisions or interactions for medical products.

The clinical trials are regulated by the Medicinal Products Act[36] and in more detail by the regulations of the Minister of Social Affairs. The regulation of clinical research is in full compliance with the respective EU legislation and stipulates that no clinical trial of a medicinal product shall commence without the approval of a committee.

There is a commission to deal with veterinary aspects (under Ministry of Agriculture of Estonia[37]) and the Estonian State Agency of Medicines[38] looking after medicines.

For medicinal products for gene therapy or somatic cell therapy, immunological medicinal products or medicinal products containing genetically modified organisms, the review period by the committee can be extended.
Authorisation for the conduct of a clinical trial of a medicinal product is granted by the State Agency of Medicines. Authorisation for the conduct of a clinical trial of a veterinary medicinal product is granted in agreement with the Ministry of Agriculture.

In the case of a clinical trial involving the use of medicinal products for gene therapy or somatic cell therapy, immunological medicinal products or medicinal products containing genetically modified organisms, the State Agency of Medicines shall decide on the grant of authorisation for a clinical trial within ninety days after receipt of the application. If the State Agency of Medicines deems it necessary to obtain the opinion of a scientific body or other body outside of the Agency, the term for grant of approval shall be extended. Such clinical trials shall not be commenced before obtaining written authorisation of the State Agency of Medicines.

There is no direct link to the GMO legislation either contained use or deliberate release. There is also no link established between the CA for the GMO aspects and those responsible for product review (veterinary/human medicine). So far no clinical trials with GMOs or gene therapy have been conducted.

3.6.2. Clinical trials: contained use vs. deliberate release

Estonia	
Contained use:	Both are possible. No experience yet.
Deliberate release:	

3.7 Finland

[35] Geneetiliselt muundatud mikroorganismide suletud keskkonnas kasutamise seadus (RT I 2001, 97, 603), amended by (RT I 2002, 61, 375) & Geneetiliselt muundatud organismide keskkonda viimise seadus (RTI, 27.04.2004, 30, 209)
[36] Medicinal Products Act (passed 16 December 2004, RT I 2005, 2, 4)
[37] www.agri.ee
[38] www.sam.ee

3.7.1. Legal framework

Several clinical trials investigating GMOs and gene therapy have been conducted in Finland. No applications for trials on somatic cell therapy have been submitted so far.

Written authorisation, as described in Directive 2001/20/EC, is required before commencing a clinical trial[39] on gene therapy, GMOs or somatic cell therapy. The procedure, application for authorisation of a clinical trial, is principally similar for all trials.
In case of gene therapy, GMOs and somatic cell therapy there are two specific rules, written authorisation instead of notification and longer periods of time (90 days compared with 60 days) as described in Directive 2001/20/EC, allowed for the competent authority to evaluate the application.

When evaluating applications for trials on gene therapy, the Agency has so far always had to ask substantial additional information on the medicinal product and its safety. As a result, trials on gene therapy are usually accepted only after several months, as the applicant has so far needed considerable time to answer the questions posed by the Agency.

Before conducting any research on GMOs, the investigator must have permission as stated in Gene Technology Act No. 377/1995[40].

The Gene Technology Act also establishes the Finnish Board for Gene Technology. In addition to being a national authority, the Board functions as a competent authority towards the European Community, processing notifications concerning the use and release of genetically modified organisms as defined in Directives 90/219/EEC and 2001/18/EC and responding to them within its authority to make legally binding decisions. The Board aims to ensure safe and ethically acceptable use of gene technology and to prevent any harm gene technology may inflict to human health, animals, property or the environment. Its priorities include processing notifications, issuing instructions and regulations, acting as a registration authority, preparing opinions and recommendations, monitoring, restricting or prohibiting the use of potentially dangerous organisms and imposing administrative sanctions to ensure its provisions are complied with.

So far all clinical trials have been considered as contained use. Deliberate release has not been evaluated as an option. Contained use requires either a notification or an application for a permit depending on the class before the activity can start.

Separate from the notification process under the Board for Gene Technology a different review is conducted by the National Agency for Medicines (see before) concerning the medicinal aspects and yet a third agency is concerned with workers safety. Also on international multi-centre clinical trials the national ethical opinion is given by a sub-committee on Medical Research Ethics[41]. All reviews run independently from each other. The Board focuses on environmental aspects, but the delineation is not always simple to make.

Applicants are required to provide quite detailed information, down to the level of the room of the individual patients. The Risk Assessment in particular evaluates the appropriateness of the confinement measures.

[39] Regulation 2/2004 clinical trials on medicinal products in human subjects
[40] Gene Technology Act (377/1995, as amended 490/2000 and 847/2004)
[41] www.etene.org/e/tukija/

3.7.2. Clinical trials: contained use vs. deliberate release

Finland	
Contained use:	So far all trials conducted as contained use.
Deliberate release:	No experience yet, but not excluded.

3.8 France

3.8.1. Legal Framework:

For R&D with GMO-medicinal products the “Agence Française de Sécurité Sanitaire des Produits de Santé” (AFSSAPS) is the competent authority. They operate as the unique portal for applications. For veterinary products the competent authority is the "Agence Nationale du Médicament Vétérinaire” (ANMV) which is part of the “Agence Française de Sécurité Sanitaire des Aliments” (AFSSA).

For contained use of GMOs the Ministry of Research is the lead administrative authority, delivering approvals for research projects. Both the Ministry of Research and the Ministry of the Environment share the authority. As a consequence, the advisory committee “Commission de Génie Génétique” (CGG) depends of the two Ministries and has a double secretariat depending if the use is respectively intended for education, research and development or for production. For deliberate release, both the Ministry of Agriculture and the Ministry of Environment are competent authority. Together they supervise the functioning of the advisory committee “Commission du Génie Biomoléculaire” (CGB).

The approach for clinical trials involving human gene therapy with genetically modified organisms combines 3 legal elements: regulation for clinical trials, regulation specific for gene therapy and regulation for GMO activities.

Clinical trials in general are governed by different laws and decrees, aiming to protect the people participating in the trial. As a consequence a review by a local ethics committee, called “Comité Consultatif de Protection des Personnes se Prêtant à une Recherche biomédicale” (CCPPRB), is required. In addition, the Law n° 96-452 of May 28 1996 indicates that clinical trials for gene therapy require in addition an approval by the competent authority (AFSSAPS). Furthermore the facility in which the clinical trial can be performed needs to have been approved for such purpose.

There are several laws and decrees defining the requirements for activities with GMOs. They take into account the European Directives, which are in practice applied, but for which the legal transposition of Directive 2001/18 is still pending. Contained use permits for research are delivered by the Ministry of Research in agreement with the Ministry of the Environment and upon advice of the CGG. For deliberate release typically the Ministry of Agriculture together with the Ministry of the Environment has been in charge, following the advice of the CGB. As indicated before, the interaction between the authorities in case of clinical trials is explicit in the law.
In the Law n° 96-452 of May 28 1996 there is specific reference to the contained use and deliberate release of genetically modified organisms, the involvement of the advisory bodies (CGG and CGB) as well as the interaction with the GMO competent authorities (Ministry of Research, Ministry of Environment). While this procedure is general for all human medicinal products and therapies, a specific central review for gene therapy products by AFSSAPS is provided for.

Not all clinical trials are handled in the same way. A special handling is provided for clinical trials for gene therapy, whereas vaccines and other medicinal products would be treated differently. All other manipulations preceding and following the clinical trial are considered to be contained use.

The scope of gene therapy products is very broad and includes genetic elements (e.g. plasmids, naked DNA…). Naked DNA is also considered by the CGG to be treated as a GMO. In addition genetically modified human cells would also be considered as GMO.

Clinical trial approvals are provided on a project basis. A project can be multi-centred.
Although the legal framework foresees that some clinical trials may be considered as deliberate release (depending on the potential for releasing the GMO in the environment), so far most clinical trials have been designed to be contained use. The evaluation by CGB is focussed on the circumstances that could lead to a release of containment and determining accordingly conditions that would guarantee containment, as well as evaluating the impact of a potential release.

From the standpoint of the GMO part of the procedure, the same practices apply for clinical trials irrespective if the target medicines for human or veterinary use. In the latter case, there are fewer examples and they are more often considered as deliberate release.

3.8.2. Procedural aspects

There are several documents to assist applicants in preparing an application. AFSSAPS provides to applicants a “Fiche de renseignements” which lists the main elements of the procedure as well as the information required in an application. Also CGG has developed a standard type of document to help applicants.

A single application is made to AFSSAPS covering the clinical trial aspects (pharmaceutical, pharma-toxicological, trial protocol...) as well as the GMO aspects (including information on containment, interactions with environment, information for the public, SNIF-document…). In parallel an application is made to the local ethics committee (CCPPRB).

The relevant parts of the file are transmitted to:
- CGG: for determining the risk level of the organism and appropriate containment level;
- CGB : for evaluating the risk for release and determining an appropriate containment period and tests to be performed;
- AFSSAPS advisory group, in particular the group Gene Therapy, focusing on safety and quality.

The opinion from CGB is only sought after the CGG has formed an opinion. It is noted that the CGB is mostly involved, but not always. It is possible that during the review additional questions are asked by the advisory bodies directly to the applicant and that the procedure (which normally should be completed in 90 days) is prolonged.

When taking a final decision, AFSSAPS takes into account its own evaluation, the advices of the CGG and CGB and the opinion of the CCPPRB. An approval can only be provided with the agreement of the Minister of the Environment and the Minister of Research. A single approval is provided, covering all aspects.
In cases where AFSSAPS has no internal review (e.g. clinical trials with vaccines), the same scheme is followed for the GMO and ethical aspect.

3.8.3. Special conditions

More than 60 gene therapy trials have been reviewed. Overall the requirements for a GMO clinical trial are felt to be very heavy, especially when compared to other applications for which there is no similar obligation:
- There are typically very few patients involved (the therapy targets rare diseases and they are usually limited trials at a very early stage in the development, multi-centre trials are still rare).
- Much emphasis on excluding dissemination leads to long periods for keeping patients in clinical settings which are difficult to apply (e.g. 30 days).

- Very complex dossiers require much information. Most of the files were well prepared in dialogue between applicant and authority.

There have been very few rejections of applications. The main concern was the quality of the therapeutic product. On the other hand, the conditions for monitoring and maintaining patients that are requested are very stringent. Biological tests are prescribed that have to be done to confirm that the risk of dissemination is no longer present.
By the time the advice is transmitted to the Ministry, the applications are well advanced and virtually all concerns have been addressed. As a consequence, the Ministers usually -although not always- follow the advice of the CGG and CGB.

The discussions at CGB including the main reasons for a possible rejection are included in the reports of the meetings of the CGB. Unlike for other applications with GM plants, the dossier summary and the complete advice are not available.

3.8.4. Issues

While the French approach functions as illustrated by the large number of trials, it has not been always easy to follow the information requirements and evaluation of GMOs. The Directives have not been designed for these types of applications and require adaptation to the particular case.

The difficulty of distinguishing between contained use and deliberate release is very hard. Involving both CGG and CGB covers all elements. However, the role of CGB is to advise on exclusion of any chance for release. As a consequence this is not comparable to a deliberate release evaluation and maybe extremely hard conditions are imposed which may not be necessary.

In the absence of common risk criteria and evaluations, the evaluation is left to Member States. A therapeutic agent may therefore be differently evaluated and subject to different conditions depending on the country. In fact, it is very well possible that a trial is considered contained use in one country and deliberate release in another country. This will influence the choice of developers and will particularly become difficult when multi-centre trials will be conducted.

In 2005 the French authorities sought clarification with the European Commission on the exclusion of medicinal products from the Directive 2001/18 part B requirement. Clearly all research & development activities remain within the scope of respectively contained use and/or deliberate release.

3.8.5. Clinical trials: contained use vs. deliberate release

France	
Contained use:	- All activities before and after trial - Most of the human clinical trials so far, stringent containment and monitoring conditions imposed.
Deliberate release:	All veterinary clinical trials

3.9 Germany

3.9.1. Clinical trials for human purposes

The Genetic Engineering Act (Gentechnikgesetz - GenTG), that came into force in 1990, regulates all activities with GMOs with the exception of the use of GMOs on humans (GenTG § 2 “Anwendungsbereich; (3) Dieses Gesetz gilt nicht für die Anwendung von gentechnisch veränderten Organismen am Menschen”)[42].

[42] http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf

The Federal Office of Consumers Protection and Food Safety (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, BVL) is the leading competent authority (CA) for deliberate release applications of GMOs; the local authorities (Länderbehörden) for the contained use[43]. There is a close co-operation between the BVL and the local authorities. The BVL gives advice to the Federal Government as well as the Federal States (Bundesländer) and their bodies on issues of biological safety in genetic engineering.

Clinical Trials in general are regulated by the German Drug Law (Arzneimittelgesetz, AMG) of 11th of December 1998 (BGBl. I S. 3586) and amendments, more in particular the 12th amendment (12. AMG-Novelle) of 30th of July 2004 (enforcement: 6th of August 2004)[44]. The 12th amendment is the transposition of the Directive 2001/20/EC on clinical trials and integrates requirements of the deliberate release legislation (Directive 2001/18/EC) on risk assessment.

In the AMG gene therapy medicinal products for human use are named gene transfer medicinal products (GT-MPs) and are defined in §4 (9) AMG. GT-MPs include medicinal products used *in vivo* which consist of or contain plasmid DNA, viral or non-viral vectors, oncolytic viruses or other micro-organisms carrying a therapeutic, a marker or a preventive gene to be transferred to human somatic cells via the action of the micro-organism. Gene transfer medicinal products also include genetically modified autologous, allogeneic human cells used *in vivo* and nucleic acids used *in vivo* to modify endogenous genes. Genetically modified xenogeneic cells are xenogeneic cell therapy products as defined in §4 (21) AMG.

According to §77 AMG, the Paul-Ehrlich-Institut[45] is the competent higher authority for gene transfer medicinal products and for xenogeneic cell therapy medicinal products.
The "release" of GMOs in relation to clinical trials with medicines that contain or consist of GMOs needs an authorisation by the Paul-Ehrlich-Institut, residing with the Ministry of Health (Bundesministerium für Gesundheit).

Preclinical experiments have to be conducted according to the GenTG; and performed in laboratories or animal facilities of safety levels S1 to S4 (contained use). Laboratory approval is given by the competent Gene Law authority of the German Land. 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.

The actual clinical trials involving the use of gene transfer medicinal products or genetically modified xenogeneic cells can only start after authorisation by the Paul-Ehrlich-Institut and the (leading) local ethics committee of the principal investigator.
Apart from the application to the ethics committee(s), only one application is to be submitted.
A recommendation concerning the vote of the local ethics committee used to be given by the Central Commission of Somatic Gene Therapy (CSGT) at the German Medical Association. Since about the middle of 2004, due to a moratorium of the German Medical Association, this is no longer done.

The Paul-Ehrlich-Institut evaluates the acceptability according to current standards of science (manufacture, toxicity data and preclinical testing, protocol); the ethics committees assess the ethical and medical acceptability (local competence, insurance, clinic design, and protocol).
The Paul-Ehrlich-Institut also performs the risk assessment according to 2001/18/EC (topics to be addressed overlap with those of "normal" clinical trials). Also, an opinion is asked at the Federal Office of Consumer Protection and Food Safety (BVL).

[43] http://www.bvl.bund.de/cln_027/nn_494450/DE/06__Gentechnik/gentechnik__node.html__nnn=true
[44] http://www.pei.de/nn_433704/DE/infos/pu/rechliches-pu/rechtliches-pu-node.html__nnn=true
[45] www.pei.de

Within the Paul-Ehrlich-Institut the Referat "Klinische Prüfungen" is the central point for submission, information and contact with other CAs (also European CAs). It also further coordinates the evaluation by integrating several expertise groups depending on the case. All the evaluations then form the basis for the authorisation.

Ninety days after the receipt of the valid application either the approval or grounds for non-acceptance are issued to the applicant. The applicant can react once (within 90 days), followed by a reassessment of 30 days, and then follows an approval or rejection by the Paul-Ehrlich Institute.

General guidelines are available (reference is made to EMEA guidelines, e.g. CPMP/EWP/463/97: Note for Guidance on Clinical Evaluation of New Vaccines). Further guidelines are available on request. Also, discussions between CA and applicant before submission are common and very helpful.

The trials are performed in hospitals with contained safety laboratories. Transport, storage and inactivation of GT-MPs containing or consisting of GMOs have to be performed according to the GenTG for experimental work with GMOs.

The Paul-Ehrlich-Institut may carry out inspections of the trial site in conjunction with the approval of a clinical trial. The suitability of the facility is assessed by the CA of the Länder. Routine inspections are carried out by the competent authority of the relevant German Land.

Information about clinical trials in Germany is available by the German Registry for Somatic Gene Transfer Studies and will also be available by Internet[46].
Five applications have been submitted since the implementation of Directive 2001/20/EC; 3 approved, none finished yet. The approved trials are Phase II (2x) and Phase I (1x) and are about viral vectors and genetically modified cells.

3.9.2. Clinical trials for veterinary purposes

In contrast to clinical trials for human medical purposes there are no specific regulations for clinical trials for veterinary purposes in Germany.

Clinical trials for veterinary purposes are regulated by the Genetic Engineering Act (Gentechnikgesetz) depending on the conditions either as contained use or as deliberate release.
In case of contained use the competent authorities are the local authorities (Länderbehörden), in case of deliberate release the Federal Office of Consumer Protection and Food Safety (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, BVL) is the leading competent authority. The BVL evaluates the safety of genetically modified organisms. In all notification procedures, the BVL asks for an opinion of the Central Commission for Biological Safety (Zentrale Kommission für die Biologische Sicherheit - ZKBS), which hosts experts in the field of bacteriology, virology, plant breeding, medicine and ecology, as well as industrial and environmental safety.
No specific explanatory notes or guidance have been issued.
A permit is required.
Clinical trials for the purpose of testing veterinary vaccines have been conducted.

3.9.3. Clinical trials: contained use vs. deliberate release

Germany	
Contained use:	- All preparatory activities - Transport, storage, inactivation of products - Veterinary trial conducted under containment

[46] http://www.zks.uni-freiburg.de/dereg.html

Deliberate release:	- Veterinary trial conducted under real-life situations.
Specific case	- Taken up in clinical trials regulation - Risk assessment according to deliberate release legislation

3.10 Greece

3.10.1. Legal framework

There is no direct link to the GMO legislation either contained use or deliberate release. There is also no link established between the CA for the GMO aspects and those responsible for product review (veterinary/human medicine). So far no clinical trials with GMOs or gene therapy have been conducted.

The Greek Ministry of the Environment is the CA for Directives 98/81/EC, 2001/18/EC (only for Part B) and for Biosafety protocol.
The contained use directive has been transposed with the Joint Ministerial Decision (2-7-2002/B 831/11642/1943) and the deliberate release directive with the Joint Ministerial Decision (21-9-2005/B 1334/38639/2017).
While there are quite a few contained use activities, there has been no deliberate release in the field and no clinical trial with GMOs. It is the intention to clarify the situation and provide guidelines on how to comply with the Directive. This will include the establishment of a Working Group for coordination with other Ministries, agencies, but also communication with the stakeholders. It is therefore deemed too early to decide on how clinical trials would be handled.

The National Organisation for Medicines (EOF) of the Ministry of Health & Social Solidarity is the competent authority for medicinal products. They apply the provisions of the clinical trials Directive. Upon a favourable opinion of the Ethics Committee the EOF grants the final authorisation for the study. This is the routine procedure for all clinical trials. This would also be applicable to evaluate applications for gene therapy. So far no such request has been made.
There is no interaction with other agencies, e.g. on environmental issues of GMOs.

3.10.2. Clinical trials: contained use vs. deliberate release

Greece	
Contained use:	Both are possible. No experience yet.
Deliberate release:	

3.11 Hungary

3.11.1. Legal framework

The competent authority for GMOs is the Ministry of Agriculture and Rural Development[47]. Applications for contained use or deliberate release are submitted to the Ministry of Agriculture and Rural Development. The application is forwarded to the Ministry of Environment and Water, Department of International Treaties for Nature Conservation[48] for an environmental impact assessment. The opinion by the Ministry of Environment is not binding.

The Hungarian Gene Technology Act does not include clinical trials. The contained use legislation even excludes clinical trials. The Regulation on Chemical and Environmental Safety deals with the environmental safety of GMOs.

[47] http://www.fvm.hu/main.php?folderID=850&seturl=folder&setlang=eng
[48] http://www.kvvm.hu/

According to the CA at the Ministry of Agriculture no clinical trials with GMOs have been applied for. As there have been no applications yet, the conditions for conducting clinical trials with GMOs have not been fully discussed.

The National Institute of Pharmacy[49] is the CA for clinical trials for human medicines.

Two legal documents are covering this topic:
- Decree 35/2005 (VIII. 26.) of the Minister of Health on "The clinical trials on investigational human medicinal products and on application of Good Clinical Practice", and
- Regulation (Act) XCV/2005 (VIII.2.) on human medicines.

There are no specific guidance documents in Hungarian, but the general European documents are available:
- detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities,
- notification of substantial amendments, and
- declaration of the end of the trials (EC, October 2005).

A permit needs to be applied for at the National Institute of Pharmacy. According to the National Institute of Pharmacy there have been clinical trials with GMOs.

For veterinary products the competent authority is the Institute for Veterinary Medicinal Products (IVMP)[50].

3.11.2. Clinical trials: contained use vs. deliberate release

Hungary	
Contained use:	Both are possible. No experience yet.
Deliberate release:	

3.12 Iceland

3.12.1. Legal framework

There is no direct link to the GMO legislation either contained use or deliberate release. There is also no link established between the CA for the GMO aspects and those responsible for product review (veterinary/human medicine). So far no clinical trials with GMOs or gene therapy have been conducted.

The Environment and Food Agency is the CA for GMO regulations, contained use as well as deliberate release.
So far only one deliberate release has been performed, relating to genetically modified barley.
No clinical trials with GMOs have been requested and it is open if this would be handled as contained use of deliberate release.

So far, in the absence of applications, there have been no exchanges with the authorities responsible for medicines to coordinate.

[49] http://www.ogyi.hu/
[50] www.ivmp.gov.hu

3.12.2. Clinical trials: contained use vs. deliberate release

Iceland	
Contained use:	Both are possible. No experience yet.
Deliberate release:	

3.13 Ireland

3.13.1. Clinical trials for human purposes

March 2001, the GMO (Contained Use) Regulations, S.I. No 73 of 2001, (transposition of Directive 90/219/EC, amended by Directive 98/81/EC) came into operation under Irish law.
The deliberate release legislation Directive 90/200/EC replaced by Directive 2001/18/EC was transposed into Irish Law - GMO (Deliberate Release) Regulations, S.I. No. 500 of 2003 – on the 1st of November 2003[51].

Clinical trials in Ireland are governed by the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004, SI No 190 of 2004. The Regulations transposed into Irish law the provision of Council Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use[52]. The regulations supersede the Control of Clinical Trials Acts 1987 – 1990 for clinical trials using medicinal products. However, because of the Act's definition of the conduct of a clinical trial in Article 6 (as amended), the Act still applies to clinical trials involving non-medicinal substances.

Competent authorities are:
- The Environmental protection agency (EPA)[53],
- Irish Medicines Board (IMB)[54],
- Ethics committees of the hospitals involved.

Guidance notes by EPA are available and specifically mention clinical trials as an example of a deliberate release application[55].

Applicants are to submit a dossier to each of the competent authorities. This can be done simultaneously. IMB adheres strictly to the timelines mandated in SI 190 of 2004.

At the IMB a Clinical Trials Sub-Committee meets to review all applications. This committee is a sub-committee of the Advisory Committee for Human Medicines. Again, guidance documents are available[56]. Specific reference is made to the need of a permit by EPA in addition to the "normal" documents when GMOs are involved.

At EPA the decision is taken after many consultations with other departments and experts; e.g. for veterinary medicines also the Department of Agriculture would be involved. Also, the trial site would be inspected before the trial.

One trial has been reviewed so far involving a GM virus (treatment of angina pectoris). This trial was performed at 4 hospitals. The permit contained several special conditions all to prevent escape of the GMM into the environment. The requirements were about waste management, record keeping, reporting of unsuspected events, etc. Many

[51] http://www.epa.ie/Licensing/GMOLicensing/
[52] http://www.imb.ie/inner.asp?nav=2,82&pos=1&num=1
[53] http://www.epa.ie/
[54] http://www.imb.ie/
[55] http://www.epa.ie/Licensing/GMOLicensing/DeliberateReleaseofGMOs/FileUpload,182,en.doc
[56] http://www.imb.ie/inner.asp?nav=2,82&pos=1&num=1

measurements were taken from the contained use legislation. In order to study shedding, experiments were integrated in a monitoring program with annual reporting.

3.13.2. Clinical trials for veterinary purposes

Clinical trials for veterinary purposes are reviewed by EPA and the Department of Agriculture and Food. The general legislation is the Animal Remedies Regulation S.I. No.20 of 2005[57]. This regulation is the transposition of Directive 2001/82/EC and amendments, but is covering a broader field and includes also clinical trials. No specific reference to GMOs is made.

Before an application is reviewed a permit by the Department of Health and Children is needed to comply with the Cruelty to Animals Act (S.I. No.566 of 2002)[58]. Also, the informed consent of the owner of the trial animals must be obtained before the start of a trial.
Other relevant legislation may be the Protection of Animals Act, 1911 and 1965, and the Protection of Animals kept for Farming Purposes Act, 1984.

This Department of Health and Children also inspects the trial sites. The welfare of the trial animals is subject to veterinary supervision by the Department of Agriculture and Food.

Also, the Department of Agriculture and Food issued guidelines on clinical trials for veterinary purposes.

3.13.3. Clinical trials: contained use vs. deliberate release

Ireland	
Contained use:	- Some “special conditions” e.g. waste management
Deliberate release:	- Trials with humans - Veterinary trials.

3.14 Italy

3.14.1. Legal framework

The Ministero dell'Ambiente e della Tutela del Territorio is the CA responsible for the implementation of European Directives 2001/18/EC. However, they are not involved in clinical trials. The Ministero della Salute is responsible for the implementation of European Directives on contained use of GMOs.

When GMOs are deployed in clinical trials they are regulated under the Directive 1998/81/EC for contained use. The Directive has been implemented into the Italian legislation by means of the legislative decree 206/2001, which lays down requirements for a written application-approval procedure for contained use of GMOs as applied in clinical trials. The contained use approval procedure relates to both the clinical site and the clinical use of the product. Class 1 GMOs are subjected to this procedure only for approval of clinical site.

The contained use authorisation procedure is independent from the clinical trial authorisation procedure and runs in a parallel way by a different C.A. The Competent Authority is the “Commissione interministeriale di valutazione delle biotecnologie” (Interministerial Committee for evaluation of biotechnology) seating at the Ministry of Health: Ministero della Salute, Direzione Generale della Prevenzione. The application forms for gene therapy clinical trials are available in the Ministry of Health website

[57] http://www.agriculture.gov.ie/areasofi/food_safety/SI_animalremediesRev3.pdf
[58] http://www.irishstatutebook.ie/ZZSI566Y2002.html

("notifica per l'uso confinato in applicazioni di terapia genica" - "notification of contained use for gene therapy applications"). The application form asks from the applicant all the information that is required for evaluation of a GMO activity.

In Italy all clinical trials with GMOs are treated as contained use. In most cases the risk of shedding is minimal and can be reduced by keeping the patient for a few days at the site. Furthermore contained use corresponds better to the actual practice (clinical setting) and the control measures that are in place. Deliberate release is not considered as an option.

The "Agenzia Italiana del Farmaco" (AIFA), part of the Health Ministry, is the competent authority for conducting clinical trials[59] in Italy concerning gene therapy, cell therapy, drug with GMO. In order to receive an authorisation for a clinical trial an applicant needs to pass a local Ethics Committee (reviewing ethical and scientific aspects) and an administrative review. The administrative authorisation is issued by:

- National Institute of Health (for Phase I studies);
- AIFA (for gene therapy, cell therapy, drug with GMO);
- General Director of local Health Unit (for all the other Clinical Trials).

In the case of cell therapy, gene therapy and drugs based on or including GMOs the centralised AIFA review and authorisation is a requirement before the trial can start.
All information on the trial and the GMO is included in a single information package and a single authorisation is delivered. In the case of multi-location clinical trials a coordination site is identified and they issue a single opinion. The additional sites may accept or reject that opinion.

The Istituto Superiore di Sanità (ISS) is responsible for the scientific evaluation of requests for gene and cell therapy. Whenever there are scientific uncertainties (e.g. when a new application has to be reviewed or when new information becomes available) a Commission ("Commissione per la valutazione dell'ammissibilità alla sperimentazione di fase I") that is part of the ISS will provide a scientific evaluation and advice. This is of course the case for Phase I trials, as it is the first time an application is submitted and evaluated in such detail.

When extensive information is available (e.g. Phase II and Phase III), the C.A. is AIFA with expertise from ISS. The procedure then requires only a local evaluation and administrative handling by the AIFA.

This procedure is similar for al medicinal products, including those generated by organisms, consisting of biologicals and gene therapy. In the latter case additional info on the GMO is required in addition to the stringent requirements on safety and quality. All patients are communicated and maintained in a database. This allows for routine follow-up.

3.14.2. Clinical trials: contained use vs. deliberate release

Italy	
Contained use:	All clinical trials so far.
Deliberate release:	So far, not considered to be an option. Clinical settings are considered to be incompatible with a deliberate release.

[59] Legislative Decree no. 211 of 24 June 2003 Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use (Official Gazette no. 184 of 9/8/2003, Ordinary Supplement no. 130)

3.15 Latvia

3.15.1. Legal framework

The government authority "State Agency of Medicines" (SAM) is monitored by the Minister of Health of the Republic of Latvia. It is responsible for the evaluation of medicinal products and drugs, their registration, monitoring, control and distribution management within the country.

No clinical trials with GMOs have been requested and it is open if this would be handled as contained use of deliberate release.

Recently Cabinet Regulation No 172[60] "Regulations on Conducting Clinical Trials and Non-interventional studies and Labelling of Investigational Medicinal Products, and Procedure for Conducting Inspections on Compliance with the Requirements of Good Clinical Practice " has been published which includes the implementation of the Directive 2001/20/EC.

In this regulation there are specific references for trials with gene therapy or involving genetically modified organisms:

- The evaluation period by the Ethics Committee may be extended;
- The evaluation period by SAM may be extended;
- There is an indication that the authorisation for a clinical trial involving medicinal products containing genetically modified organisms shall be issued in accordance with the normative acts on restricted use and deliberate release into the environment of genetically modified organisms. This means that the regulation for GMO activities applies too.

So far, in the absence of applications, there have been no exchanges with the authorities responsible for GMOs to coordinate.

3.15.2. Clinical trials: contained use vs. deliberate release

Latvia	
Contained use:	Both are possible. No experience yet.
Deliberate release:	

3.16 Liechtenstein

3.16.1. Relevant regulation

The contact person at the "Amt für Umweltschutz"[61] was unfortunately not available for discussion.

Contained use and deliberate release applications need an authorisation by the "Amt für Umweltschutz". The environmental risk assessment is performed in collaboration with the "Fachstelle für Biotechnologie des Kantons Zürich" (KSF), Switzerland.

The "Gesetzes vom 17. Dezember 1998 über den Umgang mit gentechnisch veränderten oder pathogenen Organismen", the "Verordnung vom 20. April 1999 zum Gesetz über den Umgang mit gentechnisch veränderten oder pathogenen Organismen" and the "Verordnung vom 27. April 1999 über die Einhebung von Gebühren nach dem

[60] Cabinet Regulation No 172 - Riga, 28 February 2006 (Minutes No 12 29.§) Regulations on Conducting Clinical Trials and Non-interventional studies and Labelling of Investigational Medicinal Products, and Procedure for Conducting Inspections on Compliance with the Requirements of Good Clinical Practice; Issued pursuant to Section 5, Clauses 6 and 15 of the Pharmacy Law

[61] http://www.llv.li/amtsstellen/llv-aus-home.htm

Gesetz über den Umgang mit gentechnisch veränderten oder pathogenen Organismen" regulate activities with GMOs[62].

No specific information for clinical trials could be collected.

3.17 Lithuania

3.17.1. Legal framework

The Ministry of Environment, Nature Protection Department is responsible for the implementation of European GM Directives. So far 5 consents for contained use facilities have been delivered, none covering a clinical trial. No deliberate release has been carried out and there are no clinical trials with GMOs at the moment.

There is nothing particular in the law on clinical trials with GMOs so any application would follow the normal procedure either as contained use or as deliberate release. There are no specific explanatory notes and guidance prepared for applicants for the clinical trials involving GMOs in Lithuania.

The applicant must receive the consent for contained use of GMOs from the Ministry of Environment[63] according to the Order on Regulation on Contained Use of Genetically Modified Micro-organisms[64] adopted by the Order No 413 of the Minister of Environment on August 4, 2003 (amended on April 29, 2004 by the Order No D1-233 and on March 4, 2005 by the order No D1-130).

For clinical trials for human use the consent from the Ministry of Health must be obtained. In the case of clinical trials involving the GMOs, additionally the consent of the Ministry of Environment to the deliberate release into the environment of GMOs for research and development purposes, according to the Order of the Minister of Environment Regulation on GMOs Deliberate Release into the Environment, Placing on the Market[65] (in force since 1 May 2004).

The applicant must receive the consent from the State Food and Veterinary Service for clinical trials for veterinary purposes and in the case of clinical trials involving GMOs, additionally the consent of the Ministry of Environment to the deliberate release into the environment of GMOs for research and development purposes.

3.17.2. Clinical trials: contained use vs. deliberate release

Lithuania	
Contained use:	Necessary for all manipulations
Deliberate release:	Seems required for actual clinical trials for human as well as veterinary purposes.

3.18 Luxembourg

3.18.1. Relevant regulation

The GMO regulations on contained use and deliberate release is incorporated in the Law of 13th of January 1997 (relative au contrôle de l'utilisation et de la dissémination

[62] http://www.gesetze.li/DisplayLGBl.jsp?Jahr=1999&Nr=104
http://www.gesetze.li/DisplayLGBl.jsp?Jahr=1999&Nr=106

[63] Law on Genetically Modified Organisms (Official Gazette 2001, No. 56 – 1976)

[64] Order on Regulation on Contained Use of Genetically Modified Micro-organisms (Official Gazette 2003, Nr. 80 – 3671)

[65] Order on Regulation on Genetically Modified Organisms Deliberate Release into Environment and Placing on the Market (Official Gazette 2004, No. 71 – 2487.)

des organismes génétiquement modifiés) amended by the Law of 13th of January 2004[66].
Laws and decrees do not specifically mention clinical trials with GMOs.

The Ministry of Health is the competent authority for both clinical trials and the GMO aspect.

The bill transposing Directive 2001/20/EC has been adopted on February 3, 2006.

No notifications have been submitted yet. In the event an application would be submitted the Law of 13th of January 1997 provides the assembly of an inter-ministerial committee to review the proposal. Also, experts might be invited even from outside Luxembourg.

No specific guidance notes are available.

3.18.2. Clinical trials: contained use vs. deliberate release

Luxembourg	
Contained use:	Both are possible.
Deliberate release:	

3.19 Malta

3.19.1. Relevant regulation

The competent authority for GMO issues is the Malta Environment and Planning Authority (MEPA). Information is available on the website www.mepa.org.mt

In Malta the contained use (Directive 90/219/EC, amended by Directive 98/81/EC) and deliberate release (Directive 2001/18/EC) regulations are transposed into national laws, respectively[67]:

- Legal Notice 169 of 2002: Contained Use of Genetically Modified Micro-organisms Regulations, 2002 (as amended by Legal Notice 194 of 2002 and Legal Notice 168 of 2004);
- Legal Notice 170 of 2002: Deliberate Release into the Environment of Genetically Modified Organisms Regulations, 2002.

Although no applications have been submitted yet, the trials would have to be performed according to the requirements of the contained use or deliberate release legislation as determined by the risk assessment for the specific GMO in the trial.

There are no guidance documents specific for clinical trials available, but normal procedure would start with an informal discussion with the applicant.

Once an application is received by MEPA, the Biosafety Co-ordinating Committee (BCC) secretariat forwards a copy of the application to the BCC members for review and assessment. The Biosafety Co-ordinating Committee (BCC) was set by means of the, Biosafety Co-ordinating Committee Regulations, 2002 (Legal Notice 290 of 2002). The main function of the BCC is to advise The Malta Environment and Planning Authority (MEPA) and the Minister responsible for Rural Affairs and the Environment on environmental implications of GMOs. It is composed of members from different ministries and expert scientists.

The Biosafety Co-ordinating Committee will discuss the methods, asks supplementary questions to the applicant and sets conditions for the trials on a case-by-case basis.

[66] http://www.legilux.public.lu/

[67] http://www.mepa.org.mt/environment/index.htm?GMOs/mainpage.htm&1

Also, the Medicines Authority would be consulted. MEPA issues the permits for the trials as well as for the facilities.

For clinical trials the Medicines Authority is the competent authority. Clinical trials are regulated according to the Medicines Act, 2003 (Act no III of 2003) amended by Act no II, 2004, and further by the Clinical trials Regulations, 2004 L.N. 490 of 2004[68], the transposition of Directive 2001/20/EC.

To conduct a clinical trial locally, one must submit applications with both the Medicines Authority and Ethics Committee and an authorisation by the Medicines Authority and a positive opinion by the Ethics Committee are required.

General guidance notes are available on the agency's website[69]. These notes make reference to the obligation to obtain an authorisation for contained use or deliberate release in case of GMOs.

Also, the Maltese Health Ethics Committee opinion is required.

3.19.2. Clinical trials: contained use vs. deliberate release

Malta	
Contained use:	Both are possible, choice to be determined based on risk assessment.
Deliberate release:	

3.20 the Netherlands

3.20.1. Legal Frame work – Competent Authorities

GMO legislation in the Netherlands is comprised in the Genetically Modified Organisms Decree implementing Directive 90/219/EEC, amended by 98/81/EC, and Directive 2001/18/EC. It is further elaborated in the "Regeling genetisch gemodificeerde organismen" ("Regeling") as published in the Law gazette of June 12, 1998, and amendments. The Decree and the "Regeling" are integrated in the "Integrale versie van de Regeling genetisch gemodificeerde organismen en het Besluit genetisch gemodificeerde organismen" of the 3rd of September 2004[70].

Applications are submitted to the National Institute for Public Health and the Environment (RIVM), Bureau for Genetically Modified Organisms (Bureau GGO) that is responsible for the administrative and technical-scientific processing of the applications. The Commission Genetic Modification (COGEM) is advisory to the Ministry of Housing, Spatial Planning and the Environment (VROM) who issues the permits.

For clinical trials on humans the CA is the Central Committee on Research Involving Human Subjects (CCMO) that resides with the Ministry of Health, Welfare and Sport (VWS).
The Medical Research Involving Human Subjects Act (WMO) of the 26th of February 1998 that regulates clinical trials was recently amended to implement Directive 2001/20/EC.
The CCMO concentrates on the ethical as well as patient related aspects (clinico-pharmaceutical evaluation).

For clinical trials with animals also the Ministry of Agriculture, Nature and Food Quality (LNV) is involved. Relevant legislation is the Animal Act (WOD) of the 12th of January 1977 en the Decree on Biotechnology with Animals (Besluit biotechnologie bij dieren) of

[68] http://www.doi.gov.mt/EN/legalnotices/2004/11/LN490.pdf
[69] http://www.medicinesauthority.gov.mt/pub/guidance_notes_ct2.pdf
[70] http://www.vrom.nl/ggo-vergunningverlening

the 30th of June 2004[71]. The "Commissie Biotechnologie bij Dieren" advises the Minister of LNV.

In case medicinal products are based on an immunological principle also the Immunological Medicinal Products Decree (BIF) of the 15th of July 1993, is involved. Batch control is performed by the Health Care Inspectorate (IGZ).

3.20.2. Procedural aspects - Conditions

The Gene Therapy Office is responsible for the coordination of all gene therapy licensing procedures. As different authorities are involved in assessing clinical trials with GMOs the Gene Therapy Office was established in October 2004 to streamline the assessment procedures and to serve as a procedural information point.

Depending on the type of trial 2 to 3 applications need to be submitted to comply with the different legislations. They are combined in one form to reduce the overlap in requested data. The applicant may also decide to split the form and send in the different parts on different points in time.
The Gene Therapy office directs the application to the authorities involved. Informal meetings with the applicant to prepare the application are an option for the applicant and will streamline the process.
In case of studies on animals (clinical trials for veterinary purposes) separate applications are submitted to each of the CAs. In this case the Gene Therapy Office has no role.

The CAs each perform the assessments, meet each other and discuss to harmonise permit conditions etc.
Because the procedures for the different permits are subject to different legislation the applicable deadlines are different. Furthermore, during each procedure additional information may be requested. Then the "procedural-clock" in this procedure stops.
The decisions/authorisations are communicated to the applicant via the Gene Therapy Office.
The executing party receives an authorisation, not the sponsor; and as a consequence, multi-centre trials need several authorisations.
Each executing party needs to appoint an environmental safety officer (MVF).

Besides gene therapy trials, the Bureau GGO considers all clinical trials where GMOs are involved for both human and veterinary purposes. Trials with GMOs also include trials with naked DNA as it cannot be excluded that experiments with naked DNA result in a GMO as defined by the EU legislation.

Clinical trials on humans with GMOs are considered to be deliberate release trials for human beings are free to move and cannot be forced to stay within the trial setting. Often other limitations (e.g. devices not present in a contained area) ask for a deliberate release assessment. In the same way, preparation/manufacturing (e.g. of somatic cells) may be performed as deliberate release with conditions imposed.
Also, when animals are involved practical reasons (e.g. number of animals) often exclude the use of a physical containment. Risk assessments therefore always consider the possibility of an escape of the GMO.
An applicant is nevertheless free to choose for a contained use application in case of a trial with animals. Preclinical trials with animals are contained use applications.

Furthermore the European Regulation 726/2004 states that for a market authorisation dossier a written consent under the deliberate release directive has to be included. The accessory risk assessment is then necessary for applications for market approval.

[71] http://www9.minlnv.nl/servlet/page?_pageid=332&_dad=portal30&_schema=PORTAL30

3.20.3. Considerations

Industry strongly asks for harmonisation between Member States. The Dutch CA is a proponent for harmonisation of gene therapy legislation (interpretation) in the EU. Therefore the Dutch CA has started a discussion in the EU on harmonisation.

Since the establishment of the Gene Therapy Office 2 applications were submitted, but many more before that.

Surveillance for the GMO aspect is done by VROM inspection that acts independently from the authorising bodies.

No problems in implementing the legislation or in compliance with the conditions have been encountered.

All legal documents are available on the internet[72] as well information about the gene therapy office[73]. This site has all necessary documents and links to legislation. It also includes extensive guidelines for researchers and sponsors with regard to the assessment by official bodies of clinical research involving gene therapeutics in the Netherlands both in Dutch and in English.
Information on the Dutch CA for GMOs in contained use and deliberate release can also be found on the internet.[74].

3.20.4. Clinical trials: contained use vs. deliberate release

The Netherlands	
Contained use:	- pre-clinical trials in animals - some animal trials when in containment (choice of applicant)
Deliberate release:	- clinical trials with humans (humans are free to move + many times additional locations needed for specific evaluation) - some animal trials when outside of containment

3.21 Norway

3.21.1. Legal Frame work – Competent Authorities

As a consequence of the Agreement on the European Economic Area, Norway follows to a large extend the Directives and Regulations applicable in the EU.

All clinical trials in Norway, both human and veterinary, must be approved by the Norwegian Medicines Agency (NMA). Clinical Trials are mainly regulated by international and national laws and the European Directive 2001/20/EC, which is fully implemented in the Norwegian Regulation[75] relating to clinical trials on medicinal products for human use, of 24. September 2003. The Regulation specifies that clinical trials that involve gene therapy or the use of genetically modified organisms as medicinal products should also be approved pursuant to Act no. 56 of 5 August 1994 relating to biotechnology. Clinical trials of medicinal products that consist of or contain genetically modified organisms may involve the deliberate release of the organism, and should be approved in advance

[72] http://www.overheid.nl/home/biotech/regels/
[73] http:/www.vrom.nl/ggo-vergunningverlening => Loket gentherapie.
[74] www.vrom.nl/biotechnologie
[75] FOR 2003-09-24 nr 1202: Regulation relating to clinical trials on medicinal products for human use

pursuant to Act no. 38 of 2 April 1993 relating to the production and use of genetically modified organisms (the Gene Technology Act[76]).

All aspects of activities with GMOs are regulated in the Gene Technology Act. This act does not exclude medicinal products.

The competent authorities for GMO in Norway is the Ministry of the Environment, represented by the Directorate for Nature Management (DR -CD/2001/18/EC) and the Ministry of Health and Care Services represented by the Directorate for Health and Social Affairs (CU-CD/98/81/EC). All contained use of GMOs in Norway requires either a notification or an approval; deliberate release requires approval.

GMO medicinal products developed in Norway will need to be approved or notified according to the Gene Technology Act and already on the developing stage be registered by the authorities. The link to contained use/deliberate release for imported products is dependent on the NMA informing the applicants about the GMO regulations or that the applicants are aware of the regulations.

Clearly all preparations involving GMOs would be considered as such and require the according measures for contained use - even if the preparation is approved by the EMEA as a medicinal product and the GMO directives no longer apply (this is possible due to the Norwegian Agreement on the European Economic Area). The question of contained use or deliberate release as applied to the specific clinical trial is, however, still open.

As far as GMOs in clinical trials are concerned, there are no explanatory notes for applicants.

In the past there has been one clinical trial involving GM adenovirus for gene therapy but there was no link made to the GMO regulation at that time. At this moment no clinical trials with GMOs are occurring. Should in future an application be made, then the first authority to be contacted would be the HealthAauthority. This would then trigger further consultation, especially between the Health and the Environmental Authority to decide on the proper handling as contained use or as deliberate release.

Clinical trials involving the use of GMOs that are not performed in a closed system with physical barriers to limit contact between the organisms and humans and the environment, and consequently not considered as contained use, are considered as deliberate release.

There are no principal objections to any of the procedures, although it is true that so far no experience with the deliberate release procedure has been accumulated. Any deliberate release requires a public hearing.

3.21.2. Clinical trials: contained use vs. deliberate release

Norway	
Contained use:	- all pre-clinical preparations - Trial performed in closed system
Deliberate release:	- Trials not performed in closed system with physical barriers to limit contact

3.22 Poland

3.22.1. Legal Frame work – Competent Authorities

[76] The Act relating to the production and use of genetically modified organisms (Gene Technology Act) – Act N° 38 of 2 April 1993

The Minister of the Environment is the Competent Authority for Directive 90/219/EEC and Directive 98/81/EC. Both Directives are implemented into national law in the Act of 22 of June 2001 on genetically modified organisms[77]. According to article 5 of this Act "a consent for the contained use of GMOs or for the deliberate release of GMOs into the environment, or the permit to place GMO products on the market shall not relieve the applicant from the obligation to obtain permits or other decisions related to any such activities required under separate provisions".

Provisions of the Act on GMOs are connected only with decisions involving GMMs and GMOs. Chapter 3 of this Act is related to contained use of GMMs and GMOs. In a publicly available register[78] supervised by the Minister of the Environment there is information on competent authorities, legal acts (both Polish and EU), procedures and documents necessary to provide for any GMO trial, guidance notes for applicants, formats of application forms, submitted applications, decisions in place and other. The application form for contained use of GMM is published in the Regulation of the Ministry of the Environment of 6 June 2002[79] laying down the formats of application forms for consent and authorisation of activities involving GMOs.

For contained use of GMMs and GMOs there are obligatory special safety conditions, including for waste disposal. Information about safety conditions in facilities are published in the Regulation of the Ministry of the Environment on 29 November 2002[80] laying down the list of pathogenic organisms and their classification, as well as the measures required for particular containment levels. Contained use of GMMs and GMOs are supervised by State Labour Inspection and State Sanitary Inspection. In the case of clinical trials with GMMs applicants are obligated to receive other decisions made by the Minister of Health, who supervises all clinical trials.

According to the “Act of 6th of September 2001 Pharmaceutical Law” the Competent Authority for clinical trials in Poland is the Minister of Health. The Act Pharmaceutical Law implements Directive 2001/20. In case of clinical trials with GMMs it is necessary to obtain the Minister's of Health consent, the Ethics Committee's opinion and consent by the Minister of the Environment for contained use of GMMs.

Currently in the Minister's of the Environment register there are no registered clinical trials with GMMs, but there are some contained use activities with GMMs and GMOs performed, which might be used in the future in clinical trials.

3.22.2. Clinical trials: contained use vs. deliberate release

Poland	
Contained use:	Both are possible, no experience yet.
Deliberate release:	

3.23 Portugal

3.23.1. Relevant regulation

The “Istituto do Ambiente” of the Ministry of Environment is the competent authority for authorisations for GMOs in contained use and deliberate release.

The relevant legislation is the Decree-Law no. 2/2001, of January 4 for contained use, and the Decree-Law no. 72/2003, of April 10 for deliberate release.

[77] OJ 2001 No 76, item 811

[78] http://gmo.mos.gov.pl

[79] Official Journal of 27 June 2002 - attachment No1

[80] Official Journal 02.212.1798 on 16 December 2002 pursuant to Article 13 of the Act on Genetically Modified Organisms of 22 June 2001

On their website the Institute explains and provides data on GMOs, primarily on GM plants[81]. No specific guidelines for clinical trials are provided.
The risk assessment to evaluate the risk for the human health (other than the patient's health) and the environment is performed by the Institute.
Although no applications have been received so far, the trial will be considered as a contained use or deliberate release application depending on the facilities and the GMO involved.

Permits for clinical trials for both human and veterinary purposes are to be applied for at INFARMED, the National Institute of Pharmacy and Medicines.
INFARMED evaluates the technical-scientific aspects.

Clinical trials for human purposes are regulated according to Directive 2001/20/EC in Law 46/2004 of August 19[82].
Guidance notes and application forms can be found on INFARMED's website[83].

The Portaria no.124/99 of February 17 establishes the requirements for clinical trials for veterinary purposes[84].

Two authorisations are needed issued by:

- the Ministry of Environment, and
- INFARMED.

Also, an inspection certificate is required.

3.23.2. Clinical trials: contained use vs. deliberate release

Portugal	
Contained use:	Both are possible depending on specification of facilities and GMO involved.
Deliberate release:	

3.24 Slovak Republic

3.24.1. Relevant regulation

In the Slovak Republic genetically modified organisms are regulated according to the 399 DECREE of the Ministry of Environment of the Slovak Republic of the 1st of October 2005, implementing the Act on use of genetic technologies and genetically modified organisms; i.e. 151 ACT of 19 February 2002 on the use of genetic technologies and genetically modified organisms, amended by the Act. No. 77/2005 Coll. as of 3 February 2005. The Act is about both contained use and deliberate release.

The Act on Drugs and Medical Devices No 140/1998 Coll. in the wording of Act No 9/2004 Coll.; Section 3: Clinical trials, does not contain specific requirements for clinical trials with GMOs. Nevertheless, cross-reference is made to the Ministry of Environment with regard to the GMO aspect.

The competent authorities are the State Institute for Drug Control[85] and the Ministry of

[81] http://www.iambiente.pt/portal/page?_pageid=33,32142&_dad=gov_portal_ia&_schema=GOV_PORTAL_IA&id_doc=5070&id_menu=5122
http://www.iambiente.pt/portal/page?_pageid=33,32142&_dad=gov_portal_ia&_schema=GOV_PORTAL_IA&id_doc=6116
[82] http://www.infarmed.pt/portal/page/portal/INFARMED/LEGISLACAO/LEGISLACAO_FARMACEUTICA_COMPILADA/TITULO_III/TITULO_III_CAPITULO_I/lei_46_2004.pdf
[83] http://www.infarmed.pt/portal/page/portal/INFARMED
[84] http://www.infarmed.pt/portal/page/portal/INFARMED/LEGISLACAO/LEGISLACAO_FARMACEUTICA_COMPILADA/TITULO_III/TITULO_III_CAPITULO_IV/portaria_124-99.pdf
[85] http://www.sukl.sk

Environment of the Slovak Republic[86] and permits are needed from both. Also, an ethics committee is involved as with other clinical trials.

Although no clinical trials with GMOs are performed so far, they would be reviewed and performed as contained use trials if they would be in laboratories or stables and cowhouses, or as a deliberate release trial if they would be carried out in the environment (e.g. patient returning home after treatment in hospital).

3.24.2. Clinical trials: contained use vs. deliberate release

Slovak Republic	
Contained use:	If trial is conducted in containment (laboratory, stable or cowhouse).
Deliberate release:	- If the trial is not conducted in containment (field) - If the treated individual can leave containment (e.g. patient leaving hospital)

3.25 Slovenia

3.25.1. Relevant regulation

So far the GMO issues have essentially been dealt with by the 3 CAs, namely the Ministry of Agriculture, the Ministry of Health and the Ministry of the Environment.

There is a legal framework[87] implementing the contained use and deliberate release. The advisory bodies consist of a Commission for GMO management, a scientific committee for contained use and a scientific committee for releasing GMOs. In these committees physicians and medical doctors are included and there are plans to extend the membership to include additional expertise.

The Agency for Medicinal Products and Medical Devices is the Competent Authority for medical products in Slovenia. There are yearly approximately 60 clinical trials reviewed, but so far none has included a GMO.

The main legal reference is the “Medicinal Products and Medical Devices Act”. This Act defines medicinal products and medical devices for use in human and veterinary medicine, the requirements for their manufacture and their placing on the market as well as the conditions and measures for assuring their quality, safety and efficacy.

The Law does not explicitly talk about GMO pharmaceutical, but they are regulated with Rules under this Act: Rules on procedures for obtaining a marketing authorisation for medicinal products (Official Journal of Republic of Slovenia no. 67/00), Rules on analytical testing of Medicinal Products (Official Journal of Republic of Slovenia no. 73/00) and Rules on pharmacological and toxicological testing of medicinal products (Official Journal of Republic of Slovenia no. 44/00). Also the recent implementation of the clinical trials directive includes the references to GMOs literally as in the Directive.

The review system is based on an initial evaluation by the State Ethics Committee. Taking into account their opinion, the local regulatory committee consisting of experts will evaluate the application and provide an advice. It is expected that at this level also GMO specific issues can be evaluated. Finally the Agency will issue the decision.

[86] http://www.enviro.gov.sk

[87] Management of genetically modified organisms act (UL RS 67/2002, 26.07.2002 stran 7635)

3.25.2. Clinical trials: contained use vs. deliberate release

Slovenia	
Contained use:	Both are possible, no experience yet.
Deliberate release:	

3.26 Spain

3.26.1. Clinical Trial approvals

Clinical trials are regulated by the Royal Decree 561/1993 of the 16th of April regulating the requirements of clinical trials and the Royal Decree 223/2004 of the 6th of February that is the transposition of Directive 2001/20/EC. The last one addresses clinical trials with genetically modified organisms. In the guidance notes (version 3 of September 2005[88]) a clear reference is made to the GMO legislation.

Veterinary clinical trials are regulated according to the Royal Decree 109/1995 of the 27th of January, supplemented with the regulation of the 1st of August 2000 and the regulation PRE/2938/2004 of the 7th of September[89]. The legislation makes no reference to the use of GMOs.

The Spanish Agency for Medicines and Health Products is the CA for clinical trials for human and veterinary purposes (Ministry of Health and Consumers). Also, an application should be made to each of the Autonomous Regions.

Guidelines, forms, etc. are available on the Agency's website. The application form addresses the nature of the GMOs involved and refers to the fact that a permit according to the GMO legislation is required.

An authorisation is needed by the Autonomous Regions, the Agency for Medicines and Medical Devices and the Ministry of Environment. In the case of animal trials with biological/immunological medicines the Agency for Medicines and Medical Devices also needs to inform the Ministry of Agriculture.

The Ethics Committee has to give a favourable opinion together with conformity of the management board of the institute/hospital. In multi-centre trials conformity of a single site is sufficient to authorise the trial. Trials on further sites only need a notification of conformity to be able to start the trial on that site.

3.26.2. GMO approvals for clinical trials

Both the contained use Directive 90/219/EC, amended by Directive 98/81/EC and the deliberate release Directive 90/200/EC replaced by 2001/18/EC are transposed into the Spanish National Law 9/2003 of the 25th of April[90], 2003, published the 26th of April 2003. Later it was supplemented with the Royal Decree 178/2004 of the 30th of January, published the 31th of January 2004. This Decree also regulates the composition and the competencies of the Inter-ministerial Advisory Committee on Genetically Modified Organisms and the National Commission on Biosafety.

According to the Royal Decree 1477/2004 of the 18th of June all activities concerning risk assessment are assigned to the Ministry of Environment.

Facilities for contained use are permitted by the CAs of the Autonomous Region, except when these facilities belong to state research centres. In these cases the Competent Authority is the Inter-Ministerial Council of GMOs.

[88] http://www.agemed.es/actividad/invClinica/docs/aclaracionesEC-0905.pdf
[89] http://www.agemed.es/actividad/legislacion/espana/veterinarios.htm
[90] http://www.mma.es/calid_amb/seg_bio/introlegal.htm

Another exception is made for permits for contained use and deliberate release in case of medicines for human and veterinary purposes and for health products and those products that by affecting the human being pose a health risk to humans, in conformity with Law 14/1986 on Health and Law 25/1990 on Medicines. Then the General State Administration is the CA.
The Inter-ministerial Council on Genetically Modified Organisms, falling under the Ministry of Environment, issues the permits. This Committee is composed of representatives of the Ministry of Environment, the Ministry of Agriculture, Fishery and Food, the Ministry of Health and Consumer Affairs, the Ministry of Economy and Trade, the Ministry of Industry, Tourism and Commerce, the Ministry of Education and Science, and the Ministry of Interior Affairs.

Clinical trials can be done as contained use or deliberate release trials. They are evaluated case-by-case. Often the applicant makes a suggestion. The particular conditions of each trial depend on the GMO and previous experience from animal or humans studies regarding bio-distribution and persistence of the GMO. Sometimes a mixture of measures of both regulations is required; e.g. in early stages contained use and later on deliberate release conditions are imposed.
In the past applications have been rejected, as the risk for humans or the environment was found to be unacceptable.

The clinical trials under contained use and deliberate release, that have been conducted so far, can be found on the Ministry of Environment's web site[91].

3.26.3. Clinical Trial surveillance

Surveillance is done by both the National Commission on Biotechnology and the Spanish Agency for Medicines and Health products.
Again, depending on the specific trial, the Ministry of Environment and/or the Spanish Medicines Agency decide whether to perform an inspection of the trial site previous to the authorisation of the trial or once it is authorised.
Usually, once the trials have started the Autonomous Regions perform the inspections.

3.26.4. Clinical trials: contained use vs. deliberate release

Spain	
Contained use:	Both are possible, depending on case-by-case evaluation, conditions depending on experience, the type of GMO, bio-distribution and persistence of GMO.
Deliberate release:	

3.27 Sweden

3.27.1. Relevant regulation

The Medical Products Agency (MPA), part of the Ministry of Health and Social Affairs, is the Swedish national authority responsible for establishing standards and requirements for the development, manufacture and sale of drugs and other medicinal products.

The Swedish Working Environment Authority (SWEA) is the competent authority for contained use of genetically modified micro-organisms (GMM) in Sweden. Contained use of other GMOs is regulated by other authorities[92]. In particular in the field of clinical trials there is close collaboration with the Medical Products Agency (MPA).

[91] http://www.mma.es/calid_amb/seg_bio/index.htm#
[92] www.gmo.nu

All aspects of contained use (e.g. preparation of the GMO) are covered by SWEA as contained use. Whenever a clinical trial project is presented as a contained use, SWEA will supervise the GMO aspect. In case where it is considered to be a deliberate release MPA follows up the procedure in line with the implementation of Directive 2001/18/EC (Swedish regulation 2002:1086), including sending the SNIF.

Applications for conducting clinical trials are submitted to the MPA and an authorisation is needed. Applicants are expected to submit a single submission, including a short introduction, an environmental risk assessment and SNIF. Immediately the appropriateness of the option (contained use/deliberate release) will be verified although in most cases applicants had pre-consultation with the authority.

When the trial concerns the use of a GMO it is decided on the basis of the type of trial, the GMO and possible effects to treat the GMO part as contained use or as deliberate release. When it is considered a deliberate release of GMO additional information concerning the consequence for the environment is required and should be provided in a separate part of the document. An assessor at the Clinical Trials Unit reviews the clinical trial of the application and an assessor at the Pharmacy & Biotechnology Unit handles the review of the effect of the GMO on the environment.

The evaluation of the GM aspects runs separate from the clinical trial demand. During this evaluation a network of agencies and experts will be involved. It is worth to mention that the "Gentekniknämnden" (Gene Technology Advisory Board) and Swedish Environmental Protection Agency, which are the central advisory bodies for all applications of GMOs, may also provide a review (submitted to the body for consideration).

Upon conclusion a single authorisation, combining the clinical trial and the GMO aspects is provided by the MPA.

The following references relate to the relevant legislation:
- Pharmaceutical Products Ordinance (1992:1752),
- Förordning (2000:271) om innesluten användning av genetiskt modifierade organismer,
- Swedish Regulation 2002:1086 (GMO regulation implementing 2001/18/EC Förordning (2002:1086) om utsättning av genetiskt modifierade organismer i miljön),
- The Medical Product Agency's provisions and guidelines on clinical trials of medicinal products for human use (LVFS 2003:6),
- Läkemedelsverkets föreskrifter och allmänna råd om avsiktlig utsättning vid klinisk prövning av läkemedel som innehåller eller består av genetiskt modifierade organismer (LVFS 2004:10).

3.27.2. Experience

In the past, clinical trials were mainly considered as contained use. Some 12 trials have been conducted. In this case each trial was considered a separate use. SWEA has not accepted contained use of GMM in clinical settings to be performed at biosafety level 1. All clinical trials that were regulated were performed at biosafety level 2. Every new use had to be notified in accordance with the contained use directive and Swedish legislation. Identical repeat trials had not occurred and multi-site trials required several contained use dossiers.

Recently there has been a policy change with a shift to considering clinical trials with GMOs as deliberate release. In this case MPA is the lead authority also for the deliberate release related procedure. SWEA remains involved as all stages before the treatment (modification, sample preparation, etc.) as well as possible follow-up (e.g. of samples taken from patients) are considered contained use. This is all part of a single procedure. It is an advantage for the users that MPA is the lead authority for the deliberate release of GMOs for clinical trials as they already are regulating other aspects of the trials.

Any uncertain case would be taken up as deliberate release. The main reason for shifting to deliberate release is the fact that there are no restrictions on treated patients. Although the risk and consequence for shedding may be very small, the fact that it can happen outside of the trial setting is deemed sufficient to consider it a deliberate release. Only trials with well known vectors/constructs, for which a lot of experience is available, might be considered contained use.

With a limited experience in both approaches, it still looks awkward to consider the trials as deliberate release. Yet, both approaches seem to result in similar level of measures and guarantee safety for humans and the environment.

Most of the trials involved adenoviruses and one case was mentioned that the Swedish authorities at that time considered as contained use and the Irish authorities as deliberate release. In comparing the analysis and measures, the actual trial conditions were very similar.

The deliberate release approach offers some disadvantages:
- the demand for information is more onerous,
- it gives a wrong perception for an activity that occurs almost entirely in a closed and controlled environment.

On the other hand it might be required for some special vectors and organisms that persist or could have an important effect outside of the patient. A case of a clinical trial with poxviruses is indicated where patients had to change bandage after leaving the hospital.

So far the definition of GMO in relation to clinical trials follows that indicated in the GMO Directives. It is further discussed if other vectors, e.g. plasmids, should also be covered, but this is not the case at the moment.

3.27.3. Clinical trials: contained use vs. deliberate release

Sweden	
Contained use:	- Most clinical trials in the past, now only for specific and well documented cases
Deliberate release:	- Human trials with risk that patient leaves setting - Any uncertainty about the trial.

3.28 Switzerland

3.28.1. Relevant regulation

The Federal Coordination Centre for Biotechnology of the Bundesamt für Umwelt (BAFU) is the entry and exit point for all notifications and licence applications under the Ordinance on the Contained Use of Organisms and the Ordinance on Occupational Safety in Biotechnology. The Coordination Centre affects any company, public or private organisation that carries out activities involving the contained use of genetically modified or pathogenic organisms.

In the GMO regulation (Gentechnikgesetz) no particular indications are provided.

Since 2 years a unified procedure has been put in place, in which Swiss Medic is the lead authority. A single application is entered and this is circulated to different agencies, including to BAFU. They look in particular to containment measures, waste disposal, etc.
The “Verordnung über die Bewilligungen im Arzneibereich” (AMBV) excludes GMOs and gene therapy products from a limited personal use exemption that applies to other medical products.

This approach follows the logic that a clinical trial is a particular case (neither contained use, nor deliberate release). Given the specifics it is perceived as being more related to contained use.

A limited number of gene therapy trials have been conducted in Switzerland. The "Verordnung über klinische Versuche mit Heilmitteln (Vklin)" describes the specific information that is required to obtain a consent for a clinical trial involving GMMs and gene therapy. In particular a risk assessment for human health and the environment, as applicable to a GMO, is required. The opinion of BAFU is required for Swiss Medic to issue a consent.

Most relevant legal references:
- Bundesgesetz über die Gentechnik im Ausserhumanbereich (Gentechnikgesetz, GTG) vom 21. März 2003 (Stand am 5. Juli 2005)
- Bundesgesetz über Arzneimittel und Medizinprodukte (Heilmittelgesetz, HMG) vom 15. Dezember 2000 (Stand am 20. Januar 2004)
- Verordnung über klinische Versuche mit Heilmitteln (VKlin) vom 17. Oktober 2001 (Stand am 7. September 2004)
- Verordnung über die Bewilligungen im Arzneimittelbereich (Arzneimittelbewilligungsverordnung, AMBV) vom 17. Oktober 2001 (Stand am 7. September 2004)

3.28.2. Clinical trials: contained use vs. deliberate release

Switzerland	
Contained use:	All preparatory phases
Deliberate release:	-
Specific case	Considered to be a separate category taken up in clinical trials regulation.

3.29 United Kingdom

3.29.1. Legal Framework – Competent Authorities

In the United Kingdom clinical trials with GMOs are regulated by two sets of legislation:

1) The GMO legislation:
- The Genetically Modified Organisms (Contained Use) Regulations 2000 (GMO(CU)) enforced by the Health and Safety Executive (HSE) (Directive, 90/219/EC, amended by Directive 98/81/EC), that came into force on November 15, 2000; and
- The Genetically Modified Organisms (Deliberate Release) Regulations 2002 (GMO(DR)) enforced by Department of the Environment, Food and Rural Affairs (DEFRA) (Directive 2001/18/EC), that came into force on October 17, 2002.

2) The Medicines legislation:
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (the Clinical Trials Directive 2001/20/EC), which is enforced in the United Kingdom by the Medicines and Healthcare Products Regulatory Agency (MHRA). It came into force May 1, 2004.

HSE has the lead responsibility for regulation of the safety (to humans and the environment) aspects of activities involving GMOs in containment. DEFRA and the Scottish Executive are joint competent authorities, scrutinising the relevant notifications. Enforcement of the Contained Use Regulations is only dealt with by HSE.
The Deliberate Release Regulations are administered by DEFRA. DEFRA and the Scottish Executive are lead competent authorities, with HSE joint competent authority covering risks to human health. Application for consent to release a GMO under the Deliberate Release Regulations can only be made to DEFRA. Once made the

application is forwarded to HSE (to scrutinise and agree on matters relating to human health and safety) and the Advisory Committee on Releases to the Environment (ACRE).

Both HSE and DEFRA are part of the Joint Regulatory Authority (JRA), ensuring close collaboration in all matters.
Also, the Scientific Advisory Committee on Genetically Modified Organisms (Contained Use) (SACGM (CU)), a non-statutory body, provides technical and scientific advice to the United Kingdom CAs.
Ethical approval is required by the Local Research Ethics Committee (LREC), and by the Gene Therapy Advisory Committee (GTAC; a Multi-centre Research Ethics Committee).
GTAC considers only patient safety. Other agencies, such as HSE, MHRA and SACGM (CU) have representatives in the GTAC.

GM vectors used in gene therapy are also classified as biological agents according to the Control of Substances Hazardous to Health Regulations (COSHH) 2002. However, if the gene therapy project risk assessment is carried out for the purposes of the Contained Use Regulations there is no need for the process to be repeated for COSHH. Similarly, if notification of the activity is made under the Contained Use Regulations there is no requirement to notify the activity under COSHH as well.

Regulations / guidance / forms can be found on the internet[93].

3.29.2. Scope

The essential difference between the contained use and deliberate release regulations is whether there is intention to release a GMO or if the action is expected to cause a GMO to be eventually released into the environment. This depends on the GMO's characteristics, such as: replication ability, attenuation level, possibility of shedding, survival outside.

Rigorous environmental risk assessments (ERAs) are required for all contained use and deliberate release activities. Clearly, if the GMM is to be released into the environment under deliberate release regulations, then a far more detailed ERA will be requested.

All gene therapy projects so far have been contained uses. A small number of vaccine trials have been deliberate releases.
Some applicants have preferred to deal with the trial as a deliberate release (e.g. trials with vaccines). Firstly, this covers any possible introduction, although maybe not intended. Secondly, it allows for understanding the risk assessment that needs to be prepared by the time a Market Authorisation may be sought. The main disadvantages seem to be the more complex procedure as well as the different level of confidentiality.

Applications with naked DNA (other than proviral cDNA) are not included in accordance with the definition of GMOs in the EU Directives. Other provisions (e.g. Control of Substances Hazardous to Health – COSHH) may impose safety measures for biological agents.
Modified human cells are included and mostly are considered class 1 organisms, as they do not survive outside the culture conditions. Non-modified human cells are not considered as GMO.

3.29.3. Procedural aspects - Conditions

The contained use regulations regime itself is self-regulating with the Competent Authority providing a challenge function. The main requirements:

[93] http://www.defra.gov.uk/environment/gm/regulation/index.htm
http://www.hse.gov.uk/biosafety/gmo/information.htm
https://www.hse.gov.uk/forms/genetic/index.htm
http://www.advisorybodies.doh.gov.uk/genetics/gtac/index.htm
http://www.advisorybodies.doh.gov.uk/genetics/gtac/gtacsop.pdf

- require risk assessment of activities involving genetically modified micro-organisms and activities involving organisms other than micro-organisms. All activities must be assessed for risk to humans and those involving GMMs assessed for risk to the environment;
- introduce a classification system based on the risk of the activity independent of the purpose of the activity. The classification is based on the four levels of containment for microbial laboratories;
- require notification of all premises to HSE before they are used for genetic modification activities for the first time;
- require notification of individual activities of Class 2 (low risk) to Class 4 (high risk) to be notified to the Competent Authority (which HSE administers). Consents are issued for all Class 3 (medium risk) and Class 4 (high risk) activities. Class 1 (no or negligible risk) activities are non notifiable, although they are open to scrutiny by HSE's Specialist Inspectors who enforce the Regulations.

The vast majority of the trials (90%) are classified as level 1 activity that does not require a notification to HSE, provided that the premises are already notified for class 1 activities. In these cases, MHRA and GTAC still need to approve.

The strict application of the contained use regulation leaves great responsibility to the applicant. However, in hospitals checks and balances are in place to ensure proper assignment (several bodies check procedures and perform inspections in relation with, amongst others, liability and insurance).

With very tight conditions and controls on early trials, experience and data is collected to allow for reasonable conditions. When evaluating containment all information on the fate and behaviour of the organism is taken into account. The fact that a patient can leave the setting is included, but is in itself not considered to be an indicator of a release.

Although in a contained use setting, patients cannot be obliged to stay for the entire trial. In practise this has never caused a problem as the duration of the trial is kept to a minimum, the compensation of volunteers is paid only after finishing the trial and often the treatment is the last resort for that particular patient.

In view of an application for product registration, EMEA accepts a thorough risk assessment equivalent to a Directive 2001/18/EC part B risk assessment, regardless of the trials being performed under this Directive or not. Confidentiality might cause a problem in relation to information to the public.

Applications need to be submitted separately to the CAs involved and will result in separate permits/consents.
Multi-centre trials may require only one notification (one to each of the CAs), if they are managed centrally.

For applications involving veterinary medicinal products containing or consisting of genetically modified organisms (GMOs) the applicant is advised to contact the Veterinary Medicines Directorate (VMD) for advice. Again, both contained use and deliberate release regulations are used. Any medicinal trial in animals involving the deliberate release of GMOs into the environment requires both an ATC and a Part B Experimental Release Licence, which is issued by the GM Policy Unit of DEFRA under Directive 2001/18/EC. The part B experimental release licence will be required before a trial may start.

3.29.4. Inspections

HSE performs inspections. Since the facility for clinical trials is usually an active research centre, these inspections cover all activities and are carried out routinely.
Also the Medicines Agency carries out inspections which are related to the product quality and patient safety.

3.29.5. Considerations

Clinical trials do not fit easily into either of the GMO regulations, but one can work with them. The classification in the different risk classes for contained use or the application of the deliberate release regulations eventually results in similar practical working conditions (e.g. waste is always treated as clinical waste, the facilities offer the same containment measures…). The suggestion was made to draft a separate regulation for clinical trials.

Multi-centre trials in different countries (e.g. for rare cancers) pose difficulties to companies in performing trials in different conditions, according to different legislations.

Some companies perceive the European regulations as making it impossible for conducting Phase III trials within the European Union, although the new United Kingdom guidance on multi-centre trials is now allowing phase III trials to be conducted in the United Kingdom. Expansion to cover sites across Europe will be difficult under the current system, particularly as there is little consistency in approach across Europe.

Another burden in development is the hospital pharmacies that have to comply with strict rules not allowing micro-organisms. This could be incompatible with GMO therapy products.

3.29.6. Clinical trials: contained use vs. deliberate release

United Kingdom	
Contained use:	If no intention to release and action is not expected to cause GMO to be released in environment. Argumentation depends on GMO's characteristics, such as: replication ability, attenuation level, possibility of shedding, survival outside.
Deliberate release:	If intention to release or action expected to cause eventual release. The fact that a human patient can leave a hospital setting is not considered an argument per se to determine that a trial is a deliberate release.

4. Analysis of options and points for attention

4.1 GMO Approach

Comparing the approaches taken in the different Member States reveals that there are several options being developed and used in order to address the safety aspects of GMOs in relation to human health and the environment.

Clinical trials are already subject to oversight, both at the local level and in most cases at national/central level. In particular trials with gene therapy tend to be heavily scrutinised. The routine review according to the clinical trials Directive ensures patients safety and in most cases would address operator safety. The additional concern for GMOs is related to impact on the environment and human health in general.

Facilities where clinical trials with GMOs are conducted are usually involved in other research phases (e.g. preparation of material, pre-clinical trials, etc.) Such phases would in any case be considered contained use, requiring a specific GMO authorisation. As such there is already a basis for oversight and control.

4.1.1. Contained Use

Most of the Member States take or took contained use as the initial approach. Clinical trials in a hospital room setting seem to correspond better to the definition of "containment" than to the typical picture of a "deliberate" release. Two elements are important:

- There is usually no intention to release the organisms (so clearly any release would not be "deliberate")
- There are typically physical and biological barriers to limit exposure of the environment and the public (e.g. hospital rooms and animal housing).

The survey illustrated that contained use is typically applied for:

- Animal trials in containment;
- All preparatory phases;
- Human trials in containment with limited or no risk of shedding.

Only few Member States treat all trials as contained use, most offering a case-by-case evaluation to verify if deliberate release would be more suitable. Italy so far has excluded deliberate release as an option for gene therapy trials. France, on the other hand, has a combined evaluation for both contained use and deliberate release elements (by the respective advisory committees) that so far has led to setting stringent conditions to achieve and control containment.

Whenever the contained use approach was followed, there were still important differences in the application:

- For instance the scope of the approval typically covers a facility with a specified containment level as well as a particular activity with an organism. The contained use Directive then provides for different procedures depending on the risk class and first use/repetition. The clinical trials approach presents a case-by-case analysis. As a consequence, some CAs (e.g. Belgium, France, Italy) also perform the GMO contained use evaluation and permitting on a case-by-case basis. Others adhere to the indications of the Directive and for instance accept that in case of a risk class 1 application the risk assessment remains with the applicant (e.g. United Kingdom). This is felt not to be a problem given that clinical trials are in any event traced at national and European level, that there is in those cases exchange between authorities that allows tracing of anomalies and that the contained use of such facilities is overall covered and controlled.

- It has been pointed out that it is difficult to classify the activities in risk classes. Based on an overwhelming experience, the United Kingdom authorities can state that more than 90% of the activities so far relate to risk class 1. Swedish authorities on the

other hand have by definition ruled out class 1 as an option, judging most of the applications to belong to risk class 2.

From the different discussions during the survey it can be concluded that it is technically feasible to develop a medicinal product purely based on contained use trials. While the medicinal products directives for both humans and animals require that deliberate release part B information is provided as well as any approval from a CA, it has not been indicated that this would be a condition as such. Clearly a commercial application needs to be accompanied by the specific GMO environmental risk assessment and all supportive data and documents, yet it cannot be excluded that this information is developed without prior deliberate release. Some CAs remarked that it might be difficult for an applicant to anticipate all elements and that postponing a detailed ERA until the commercial stage may not be the best strategy. Since it is required that during the commercial review the CAs responsible for Directive 2001/18/EC are consulted, it might be advisable to get their opinion already during the clinical trial phases.

4.1.2. Deliberate release

For some trials, no real containment measures are or can be put in place. This is the case when treating certain animal species in realistic farm and field conditions. Some trials with pets have been indicated where the animals leave the trial setting to return home with the owners. A similar rational is maintained for ambulatory trials, where patients only stay shortly in the actual hospital setting.

Tthis has been extended to the possibility that human patients can always decide to leave containment even if there is a condition that this should not occur during a certain period. Others question if this is in itself sufficient reason to opt for deliberate release or if it should rather be considered as an elemen in the risk assessment. In fact it may turn out that even if the patient leaves before termination of the indicated period (which is deemed very unlikely in any event) that this does not necessarily lead to exposure e.g. because there is no risk for shedding.

Deliberate release allows for a trial-by-trial evaluation. It also includes a detailed ERA intended as a preparation for an eventual placing on the market. Apparently some applicants have opted for deliberate release in order to be covered in case of a non-intentional release as well as for obtaining indications on the ERA.

A major disadvantage seems to be the confidentiality and public involvement provisions. Information on patients and treatments, as well as the development of medicinal products is governed by tight confidentiality rules. For GMOs there is an obligation and a strong preparedness to be transparent. For this reason, some applicants have preferred to operate as contained use which provides more flexibility in handling information.

4.1.3. Third option

Some Member States, recognising the specific nature of clinical trials with humans, have opted for a third option. In this case neither the contained use nor the deliberate release procedures are followed as such. A particular provision is added to the clinical trial Directive implementation, in order to ensure that a GMO evaluation is carried out. The relevant GMO advisory bodies are involved in the review, but many of the GMO specific procedural aspects are not observed (e.g. information to the public, GMO notification to the Commission, circulation of SNIF).

Austria excluded human clinical trials that occur in containment from its GMO legislation. It is fully managed by the authority responsible for clinical trials. A similar situation is in place in Germany. In France, the different laws support an integrated approach, yet the GMO procedural aspects remain in place.

4.1.4. Overview

Based on the database collected in the project, an attempt was made to picture the relative importance of the different approaches in the EU. For the deliberate release only those trials were marked that were taken up in the JRC GMO database, as this confirms that the procedure has been followed.

Figure 7 shows the effective contribution of each approach in the Member States. So far 13% of the clinical trials have been conducted as deliberate release. However, gradually more authorities seem to be convinced that certain trials require a deliberate release approach, so the relative importance may increase. On the other hand, it should be noted that the figure for contained use may be underestimated, given that certain risk class activities might not be recorded as a separate activity.

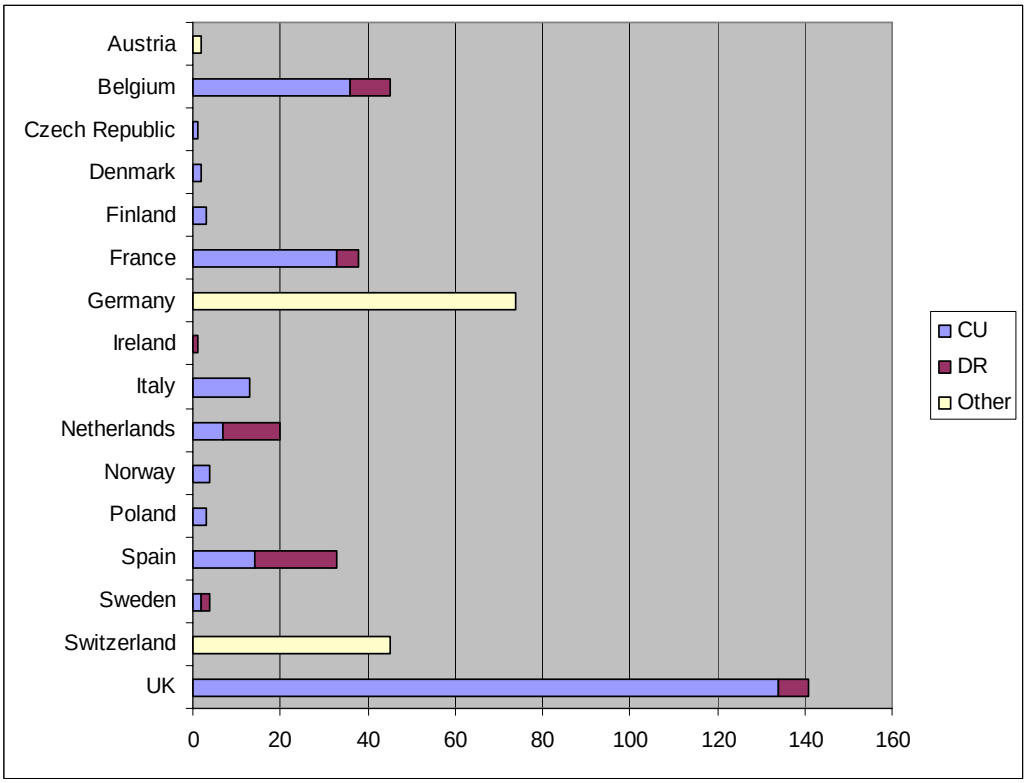

Figure 7 Contribution of Contained use (CU), Deliberate Release (DR) and other approaches for GMO clinical trials in the specified countries.

4.2 Regulatory Models

In this section the different regulatory solutions are briefly summarised according to 4 different models. It should be noted that in a country different solutions may be applicable depending on the type of application. For instance the way a veterinary clinical trial is treated may be different from a human clinical trial, and even for human clinical trials there may be differences between gene therapy and vaccination trials.

4.2.1. Co-existence of Requirements

While countries have implemented the GMO Directives (contained use and deliberate release) and the clinical trials Directive, in some cases the possibility of clinical trials with GMOs has not been considered yet. This is partly due to the absence of such trial applications and the focus on the more advanced applications with genetically modified crops and food products.

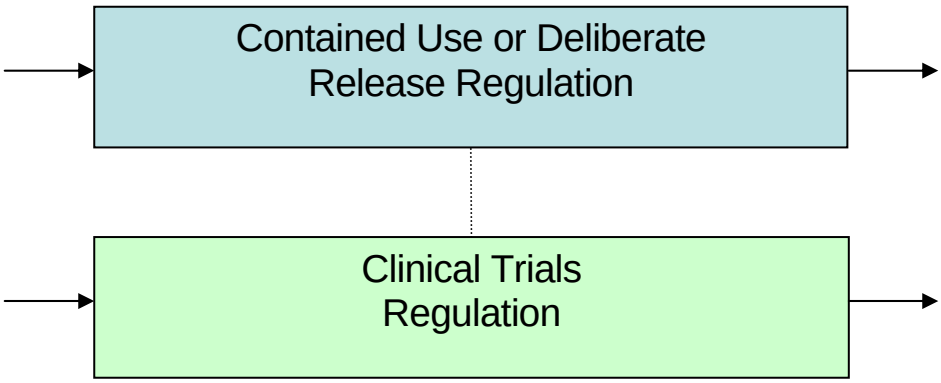

Figure 8 Model for co-existence of requirements between GMO Regulation and Clinical Trials Regulation.

From more experienced countries, it is clear that a good interaction between authorities (GMO and medicinal products) helps to clarify the requirements, to streamline the process and to avoid that applicants unintentionally may not comply with all regulations. A common understanding between all authorities involved certainly is beneficial to support the regulatory process.

Based on the feedback from the countries this seems to be the situation in Cyprus, Estonia, Finland, Greece, Hungary, Iceland, Latvia, Liechtenstein, Lithuania, Luxembourg, Poland, Portugal, Slovenia.

4.2.2. Cross-referencing

Some countries keep both regulatory aspects and procedures completely separated, while including cross-references between GMO and clinical trial regulation at different levels. While each authority remains competent for a specific regulatory area, cross-referencing and/or integration avoid omission of a critical regulatory step.

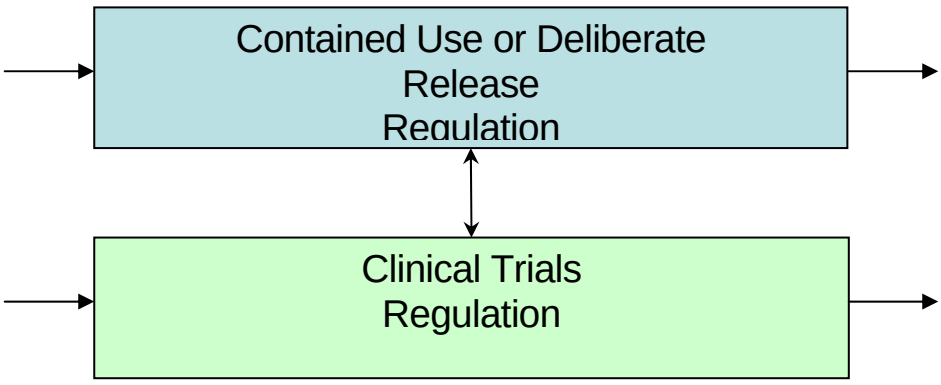

Figure 9 Model for cross referencing between GMO Regulation and Clinical Trials Regulation.

An initial level is the legal framework, in which references to other obligations are inserted. For instance in implementing the clinical trials Directive, some countries include a particular reference to the national GMO legislation, indicating that a permit or consent pursuant to that legislation may be required additionally.

Also in guidance notes to applicants or in introductory contacts with authorities, an applicant may be directed to other requirements. In some cases, this is included in the submission form, making the reference between different submissions explicit.

Finally, in some cases the consent or authorisation may include a reference or condition, stating that in order to perform the trial also other approvals need to be obtained.

During the evaluation there can be exchange between the different authorities. In some cases, there might even be a mutual representation at advisory bodies or a systematic exchange of information, enabling the respective authorities to monitor and track developments. This could for instance be helpful if a risk class 1 activity would not lead to a notification, but would be noticed as a clinical trial and allow the GMO CA to remain informed on the activities.

In this case, both legal frameworks remain independent and each case can be evaluated separately for both aspects. Permits will be issued separately, and it is the responsibility of the applicant to obtain all necessary permits. During the process the applicant is directed to ensure that all obligations are fulfilled.

This model has been well developed in Denmark ensuring exchange between the different authorities and clear indications before and during the procedure, as well as a reference in the permit.

In Ireland, applicants are to submit a dossier to each of the competent authorities. Guidance documents are available that make specific reference to the need of a permit by EPA when GMOs are involved in addition to the standard clinical trial documents.

In Italy, the contained use authorisation procedure is independent from the clinical trial authorisation procedure and runs in a parallel way by a different C.A. Still the application form for clinical trials asks from the applicant all the information that is required for evaluation of a GMO activity. Furthermore, the CAs are represented in advisory bodies, so that an exchange is guaranteed.

The Maltese Medicines Authority has posted general guidance notes for clinical trials applicants on the agency's website. These notes make reference to the obligation to obtain an authorisation for contained use or deliberate release in case of GMOs.

In Norway, the Czech Republic and in the Slovak Republic, the national clinical trials regulation specifies that clinical trials that involve gene therapy or the use of genetically modified organisms as medicinal products should also be approved pursuant to the laws relating to biotechnology.

A very much-elaborated system with different CAs has been put in place in Spain. While separate permits are required for the clinical trial and GMO aspect, the applicant receives very clear indications on all procedures involved.

Finally, the United Kingdom offers an example of keeping the regulatory procedures separate while ensuring interaction and referencing. Guidance notes to applicants from the different CAs, strict observance of contained use and deliberate release procedures, exchange between authorities and representation at advisory bodies, and ensure a smooth user-friendly system that provides guarantees for safety and compliance.

4.2.3. Single submission & Multiple permits

Some countries maintain separate legislation and procedures, but have integrated the review process in a single procedure. Typically the applicant will then submit a dossier, which combines different parts as relevant for the different legislations. In fact this can be more than the clinical trial and GMO part, if for instance animals are concerned.

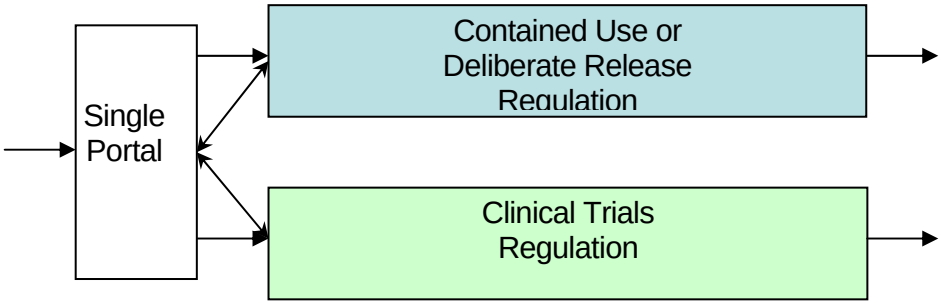

Figure 9 Model for Single application & multiple permits for GMO and Clinical Trials Regulation.

The single application is provided to a central office, which then takes care of distribution of the different parts to the respective authorities and may coordinate the process further. At the conclusion of the review the applicant will receive the independent permits/consents from the respective CAs.

To a certain extend this approach is a practical arrangement and does not necessarily require legal provisions. In fact the different CAs remain competent, reviews can follow the normal legal requirements and independent permits are delivered.

It is critical that during this process interaction between the applicant and the different reviewing agencies is possible. A short communication line is important to ensure that technical aspects can be addressed correctly and quickly.

The Gene Therapy Office in the Netherlands provides such a central coordination for human clinical trials. They interact with the applicant and contact persons in the involved Ministries to direct an application through the process. The exchange between authorities facilitates harmonisation of permit conditions. At the end independent permits are provided.

4.2.4. Single submission & single permit

There are also cases where all GMO and clinical trial related elements are integrated in a single procedure, requiring a single application and resulting in a single permit that will cover all aspects. Given that this requires a special indication of competencies and recognition of the single permit, specific legal provisions might be required.

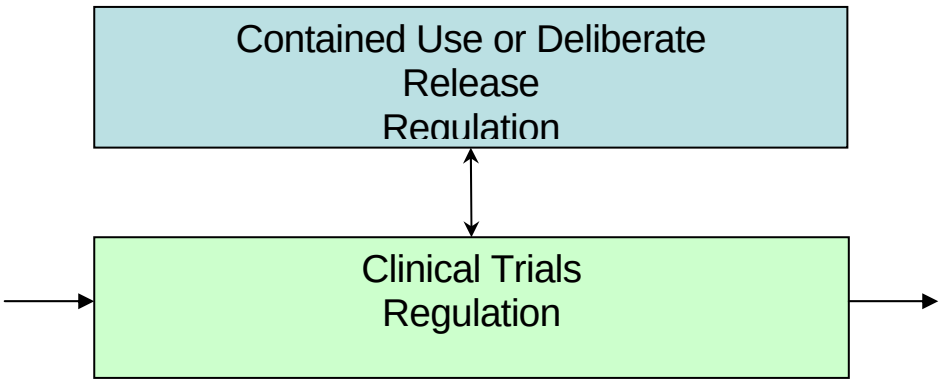

Figure 10 Model for Single application & single permit for GMO and Clinical Trials Regulation.

In most cases, the procedure involves consultation between the different CAs and review by the respective advisory bodies. The decision making process has to be clearly identified in order to ensure that the different elements are properly taken into account.

For those human clinical trials that are considered deliberate release in Belgium, a single application is submitted, and upon including all the advices, the Minister of Public Health will deliver a single permit.

In France, applications for gene therapy trials are submitted as a single dossier to AFSSAPS. The relevant parts are distributed including to the GMO advisory commissions. When taking a final decision, AFSSAPS takes into account its own evaluation, the advices of the CGG and CGB and the opinion of the CCPPRB. An approval can only be provided with the agreement of the Minister of the Environment and the Minister of Research. A single approval is provided, covering all aspects.

Also in Sweden a single procedure is in place for human clinical trials with GMOs that are considered as a deliberate release. Upon conclusion a single authorisation, combining the clinical trial and the GMO aspects is provided by the Medical Products Agency.

Since 2 years a unified procedure has been put in place in Switzerland, in which Swiss Medic is the lead authority. A single application is entered and this is circulated to different agencies.

In some cases this has led as far as creating a separate category of GMO trials which are completely excluded from the standard GMO regulation (Austria and Germany). In the case of human clinical trials with a GMO in Austria, the applicant still has to submit two applications, but will receive a single permit.

4.3 Points for attention

In this section some remarks and observations recorded during the project are grouped to reflect points of attention. They do not specifically address risk or a regulatory consideration, but indicate an area where improvement should be considered.

4.3.1. Risk assessment methodology

The risk assessment methodology as routinely applied for GMOs reveals to be difficult for cases of clinical trials. A major issue is related to the risk of shedding after application. While this could be source of dispersal of the GMO, it is not evident if this is to be considered as a risk in itself. Some CAs indicated that the potential for shedding is sufficient to require additional measures. Others rather investigate the fate of the organism upon shedding and the potential for secondary effects before considering additional protective measures.

The same holds for the argument that patients may leave the trial setting. It has been indicated that in some countries this is considered sufficient reason to classify a trial as a deliberate release. In other countries, this fact would be combined with information on the biological distribution of the GMO, survival, shedding, etc., to determine the potential impact and exposure. Also the GMO itself is often biologically contained (e.g. replication defective). Finally, an organism contained in a human or animal body could be considered as biologically contained, fulfilling the definition of contained use.

A similar concern was raised over the identification of risk class for the organism. The organisms are engineered with a therapeutic or medicinal purpose. The medical aspects, including safety, manufacturing, purity and quality, are scrutinised as part of the clinical trial preparation. They usually require a very specific delivery method in order to be effective. As a consequence many have been classified as risk class 1 in the United Kingdom. On the other hand, in Sweden they have been by default classified at least as class 2 organisms. In France, one of the main tasks of the CGG advisory committee is to determine the risk class of the organism and the activity.

When reviewing the practices, there seems to be an inversion of the order of the risk assessment procedure. In several cases it was indicated that the type of application (contained use or deliberate release) will be determined by the outcome of the risk assessment. Yet, as indicated before, the main element of decision is the presence/absence of containment measures. The risk assessment will determine the potential risk factors and uncertainties that can be addressed by additional risk management measures.

Repeatedly it was remarked that the GMO Directives have not been designed for this type of trials. It can be questioned if -just as in the case of higher plants for which an adapted format is provided- a separate specification is needed for clinical trials.

In this respect it should be emphasised that clinical trials with humans are already subject to specific and stringent control measures. The clinical trials Directive sets clear indications and in particular for gene therapy and GMOs the most stringent conditions prevail. While the focus is on patient safety, the procedures and facilities ensure to a large extend containment. In addition, since in many cases other phases require to be covered by a contained use notification or permit, the GMO aspects and safety for the environment and health are ensured.

4.3.2. Multi-centre trials

Advanced clinical trials require a multi-centre approach. While the Regulation on Medicinal Products does not require that multi-centre trials span different countries, the reality of standard clinical trials shows that developers operate in different countries. While this may be inspired by commercial motivation, it is partly related to the availability of patients that can be recruited for the trials. In particular for rare diseases, it is hard to select a relevant number of patients, thereby requiring a broader geographical distribution of the sites. While the clinical trial Directive enables multi-centre (multi-country) trials, the different GMO approaches and requirements entail additional effort and uncertainty for the applicant. A difference between contained use in one country and a deliberate release in another country multiplies the regulatory effort, while not adding to the inherent safety of the operation.

4.3.3. Application formats and documentation

As reviewed in detail before, Member States have established specific procedure either completely, partly or not at all integrating the GMO elements into the clinical trial regulation. As a consequence, while all elements are mostly preserved throughout the different applications, there are still considerable differences in presentation. An applicant who intends to perform a multi-centre, multi-country clinical trial faces an additional administrative burden of adapting to the respective format requirements. It is very much conceivable that an applicant would needs for the same trial different applications for contained use in two countries and a deliberate release in a third country.

4.3.4. Common good practices

It has been pointed out that clinical trials are governed by stringent set of rules of conduct. Furthermore in most cases standard practices for hygiene, quality, health and safety are in place. While it was questioned if these would be sufficient to cover also environmental aspects and impact on public health at large, a number of authorities pointed out that in their experience these practices were a sufficient basis for GMO safety too. Some CAs indicated that it would be helpful to share the experience of well developed practices between research groups and Member States.

An additional point was made that irrespective of the fact if the trial is considered contained use or deliberate release, the infrastructure, the persons involved in the trial and their training, the practices and special measures remain very similar.

4.3.5. Confidentiality

Regulation of medical products, both for human and veterinary use, is governed by product related confidentiality provisions. Also for clinical trials particular confidentiality provisions are in place to ensure the privacy of the patient. In contrast environmental and GMO regulation has been heralded as transparent and open for public interest. Decisions may actually require public involvement and hearings. This is even more so the case for deliberate release applications than for contained use.

As different countries observe different practices on confidentiality of information, a very scattered picture of the situation is available. In this project, difficulties were encountered in collating the table of performed trials and conflicting information had to be integrated.

Yet, it can be a determining factor for an applicant who wants to protect the information in a way similar to any other medicinal product. Once the commercial approval application is filed the EMEA confidentiality rules apply even -as it seems to be at this moment- for the risk assessment on the GMO aspects. So, the main challenge will then be to secure confidentiality during the development phase, in particular the clinical trials.

4.3.6. Scope

All countries maintain the scope of the GMO products as defined in the contained use and deliberate release Directives. This clearly covers activities with virus vectors such as Adenovirus, Retrovirus, Vaccinia virus, Herpes virus and Pox virus (total more than 60% of all trials in EU).

However, many gene therapy trials depend on other genetic delivery systems, including naked DNA, plasmids and lipofection. As indicated in the survey, these 3 methods account for approximately 17% of all gene therapy and GMO clinical trials in the EU.

Irrespective of the method, all would be covered by the clinical trials Directive. The CAs of France and the Netherlands have indicated that they extend the scope of the GMO regulation to include also naked and plasmid DNA. In particular cases, where *ex vivo* modification is performed the transformed human cells are then also considered GMO.

This difference in approach has to be seen against the discussions that are happening to define the actual active substance of the medicinal product. As indicated in section 1.2.2 gene therapy products could be genetically modified cells or a batch of ready prepared vector.

Whatever the specification of the active substance, EMEA will ensure consultation of the CAs responsible for deliberate release of GMOs for any product that falls within the scope as defined by the deliberate release Directive. If countries maintain different (broader) definitions, then this could lead not only to differences between countries but also to a disconnection at the commercial approval stage. It could be possible that a product was considered GMO during development and clinical trials and is placed on the market as a non-GMO medicinal product.

4.3.7. Perception

Several CA remarked that the image of a clinical trial is incompatible with that of a deliberate release. A hospital setting, in particular for gene therapy and clinical trials, corresponds better with a contained use approach than with a deliberate release. Also, the fact that any release would not be intentional was pointed out. Deliberate release is associated with field trials and in this respect some trials with animals seem fit to be classified as such.

As a consequence, it was observed that most CAs initially based their approach on contained use. Some, for instance Italy, still maintain this approach.

An additional concern was raised on the rather negative public connotation of deliberate release trials with GMOs. Previous deliberate release trials (mostly field trials with GM crops) have attracted considerable public and media interest. In contrast, many clinical trials have been posted on national and Commission websites without entailing so far the same type of reaction. Irrespective of the reaction, it is stressed that the involvement of the public in a deliberate release is much more elaborated. In some countries this is considered an additional burden and an important disadvantage for applicants.

5. Conclusion

This report combines information on clinical trials with GMOs, the European and national legal approaches as well as the guidance and experience from the related CAs. Overall a very good response was obtained from all Member States, which resulted in a complete overview of the EU. Furthermore, much information could be verified in publicly available sources (essentially internet). Many CAs have websites available to guide applicants and to clarify issues relating the GMO activities. In many Member States specific sections have been reserved for clinical trials.

Overall the EU is an important player, although almost 3 times more clinical trials are conducted in the USA. In the official EudraCT clinical trial database, the cumulative number of clinical trials -with and without GMOs- reported by Member States is 10514 since May 2004. In this survey almost 430 trials with gene therapy and/or GMOs were identified, showing the relative importance.

It is stressed that not all clinical trials are addressed in the same way, even within a country. Trials for veterinary medicines, trials for gene therapy and/or trials for other human medicinal use can be subject to very divergent legal requirements. No particular safety area has been identified that cannot be addressed by contained use respectively deliberate release. Both aim at protecting the environment and human health and therefore require a risk assessment preceding the activity.

Some Member States treat all trials so far as contained use, most offering a case-by-case evaluation to verify if deliberate release would be more suitable. So far 87% of the clinical trials have been conducted as contained use and the actual number may be underestimated, given that activities of risk class 1 might not be recorded as a separate activity. However, gradually more authorities seem to be convinced that certain trials require a deliberate release approach and so the relative importance may increase. The main elements that support a decision to classify a specific clinical trial as a deliberate release are:

- the open design of the trial (e.g. with large animals in farm environment or with ambulatory treatments)
- the right of a patient to leave the trial setting before completion of the control period
- the potential for shedding of GMO's.

It has been pointed out that irrespective of the legal procedure; the practice may not differ very much. An example was cited where two identical clinical trials were carried out in two countries, one being considered contained use and one deliberate release. When comparing the actual considerations and conditions of the approved trial, only circumstantial differences were noted.

The interactions between the GMO and the clinical trial regulation can be grouped according to 4 models:

- co-existence of requirements between the requirements
- cross-referencing between the regulations
- integration in a single submission and delivery of multiple permits
- integration in a single submission, single procedure and single permit.

The GMO requirements are seen as an additional burden on an area, which is already heavily regulated and scrutinised. Contained use seems in this respect more appropriate as most facilities would have more general contained use coverage including other phases of the activity (e.g. preparation, storage...).

Overall CAs welcomed the initiative by the European Commission to compile the different approaches and stressed the need for further harmonisation. Areas that need to be harmonised include:

- risk assessment methodology
- classification of organisms
- criteria for determining contained use or deliberate release
- scope of definition
- format of applications and data requirements

This harmonisation is urgently needed as developers reach advanced phase clinical trials and multi-centre trials. Facing uncertainty and multiple, scattered indications will hinder progress in this field.

Annex 1. Methodology of the study

1. Working plan of the project

The Service Contract was signed by the representative of the European Commission on November 30, 2005. Contract duration was fixed at 6 months from the date of signature.

On December 6, 2005, Perseus met with the EC contact person for the project to discuss the work plan. The Commission contact person stressed that the priority of the project was to determine the current situation in the Member States according to the objectives set down in the tender. The view of each Member State CA had to be taken into account, recognising that not all CAs may have the same level of experience in handling clinical trials. Subsequent to the meeting; an up-to-date list with the national CAs for both the contained use and the deliberate release Directive was provided.

During December and January, the primary focus was the collection of background information preparing the actual contact phase. Given the scope of the project 3 areas were documented: type of applications and main biosafety risks, regulatory frameworks and approach by CAs.

- For the type of applications publications, conference materials and sample notifications have been collected. The range of applications provided a good view on the diversity of trials and product development.
- The review of the regulatory frameworks focused on identifying possible areas of incompatibility between the approach of contained use or deliberate release and the process leading up to commercialisation of medical products. They were documented and included in the preparation for the interviews with CAs.
- The major part of the effort was taken up by the fact finding on the status in Member States. For a number of countries the status of applications was verified as well as the national legal frameworks. Indications and guidance (e.g. formats and procedures) provided by CAs to applicants was collected and analysed as far as available and possible.
- At the end of January feedback was provided to the Commission by phone.

According to the work plan a first interim report was due 10 weeks after signature of the contract, more precisely on February 8, 2006. A short Memorandum was completed on February 7 and sent to the Commission, providing an update on actions completed and planned. It was indicated that as certain Member States have opted to leave the handling of clinical trials to a different authority and/or expert group, Perseus would also contact these people in order to document the process as well as the interaction with the contained use legislation.

Between February and April, the main activity was contacting the identified authorities and collecting information (see 2.3).

On April 6, feedback was provided to the Commission and concluding actions were discussed. An interim report dated April 7, was provided according to the agreed working plan.

On May 2, a meeting was held at the Commission's office to discuss the draft final report and a draft was submitted May 16. Upon comments received from the Commission the final report was presented on June 22 and on July 3 it was confirmed that the final report was acceptable.

2. Regulatory analysis

The regulatory analysis consisted of two parts.

In the initial part, essentially the European documents were reviewed in detail for legislation relating to GMOs, to medicinal products for human and veterinary use as well as specific indications and guidelines for clinical trials. In particular the interaction between the scope,

procedures and authorisations of the different legislative areas was investigated. The main source of information was the Official Journal of the European Union.

The analysis was further elaborated based on indications by the Member State CAs and even more during a visit and interactions with the European Medicines Agency (EMEA).

The second part of the analysis covered the actual legal situation in the Member States. Much information is available either on websites of the authorities or on other sites (e.g. the Biosafety Clearing House). Unfortunately many of the documents are in the original language and therefore only to a limited extend accessible. At the same time guidelines, recommendations and/or particular formats for presenting dossiers for a clinical trial were collected. This information was used when contacting the authorities for the interviews. During these interviews and exchanges, Perseus was pointed out to additional references and these were included in this report.

3. Interviews with Competent Authorities

The national competent authorities had been identified in the project as the main source of information. Perseus acknowledged that the main challenge of this task was to get the cooperation of the interviewed. They are overwhelmed with inquiries, usually are frustrated by the limited amount of effect and have already an overfull agenda. Aiming to obtain feedback from all of the CAs, Perseus developed a contact approach based on the following principles:

- Contacts will be adapted to the time schedule of the authority and their effort to prepare and interact will be limited.
- A clear description of the project, objectives and importance of cooperation will be provided to each contact before the meeting.
- Multilingual approach given fluency in English, French, Spanish and Dutch.
- In many cases, Perseus has already established a good relationship with the authorities.
- The authorities will be able to review the result of the interaction.

This part was intended to be done based on phone calls, meetings in Brussels or visits to a limited number of Member States. Unfortunately, during the project period no CA meetings were scheduled which could have been an opportunity to meet for an interview.
Visits were scheduled in Belgium, the Netherlands, United Kingdom, and France. Other visits (Sweden, Germany and Italy) were explored but given the detailed preparatory interaction with the authorities deemed no longer necessary.
For all cases where meetings and visits were not possible, phone interviews were conducted.

All 25 Member States were contacted, including either the CA for contained use, deliberate release or for clinical trials. In addition contacts in Norway, Iceland, Switzerland and Liechtenstein were included. A list of all authorities contacted is provided in Annex 2.

The contact process ran in 3 steps:

Step 1 Introduction

In most cases it was tried to establish contact by phone and with immediate follow –up by e-mail. In the e-mail the scope of the study was indicated and the key information that was investigated, including:

- How are clinical trials with GMOs for human medical and veterinary purposes regulated?
- Are there explanatory notes or guidance notes for applicants?
- Is there a link to Contained Use / Deliberate Release/ Both (case-specific) / None
- Which is (are) the competent authority(ies)?
- Is a permit required?
- Have clinical trials with GMOs been conducted? If yes, we would appreciate indications on type of GMO's, # patients, facilities where trials were performed (including containment), waste disposal, follow-up surveillance post patient discharge including survival, persistence and discharge of GMMs, and inspection and control mechanisms (or an indication on where such information can be found).

- Any other comment/opinion/suggestion.

The initial contact helped to position the project, and to be directed to more appropriate and/or additional contact people. It is the conviction of Perseus that this direct personal contact has significantly contributed to the high response rate to this inquiry.

Step 2 Interview

Each interview started with a brief introduction of the purpose of the inquiry and stressing that the purpose of this study is to get a complete picture of the situation in EU and how different regulatory options work.
The interview was partly with prepared options (comparable to a marketing phone call) and partly with open questions. This allowed focus while leaving sufficient room for personal observations. Some people preferred to have time to prepare so that they were either left to respond in a written form or where contacted again at a later moment after having received the questions in writing.
The information was in some cases very limited, e.g. if no clinical trials with GMOs has been handled. In other cases additional information, clarifications and documents were provided. Overall the response has been very cooperative and positive about the initiative.
For each interview, a standardised report was filled out.

Step 3 Feedback

The standardised report was filed as draft 1. This draft was submitted for comments to the interviewed person either by e-mail or by fax with a request to answer before a certain deadline.

In case no answer was received the content of the report was supposed to reflect the interview. A final version was produced with an indication “no comment from interviewed person”.

When comments were received the report was adapted. If only minor changes were required, then a final version could be made with proper indication. If major changes were required the adapted draft 2 was resubmitted to the interviewed person for final agreement. Not more than 2 drafts were circulated. The information was incorporated in the country review.

4. Similar initiatives

During the project Perseus was informed of two other initiatives that covered similar aspects. As mush as possible it was tried to integrate the available information and avoid duplication.

a. EMEA inquiry

In July 2005 EMEA launched as part of a project to develop a guideline for environmental risk assessment, a survey on “Environmental Risk Assessment for Gene Therapy Medicinal Products”. The survey was provided to all Gene Therapy Working Group Members and National contact persons. These contact persons were asked to liaise with their GMO Competent Authority, as appropriate, to answer to the questionnaire. It is unclear from the feedback that was obtained during this project if and how this occurred in the different Member States.

The questionnaire aimed to map the application of contained use and/or deliberate release regulation for clinical trials with gene therapy. In particular it questioned on what basis a decision between the two approaches was made.

The outcome of the questionnaire is not publicly available.

b. Euregenethy

The Euregenethy network is supported by the European Commission DG Research/ Life Sciences strategic and Policy aspects. It gathers scientists and doctors involved in the

clinical implementation of gene transfer technology in order to help facilitate it from the users' standpoint.

In conducting its first (distinct) programme the Euregenethy network has identified additional downstream activities aiming at facilitating the development of Gene Therapy from the users' standpoint. The Euregenethy 2 is focusing on the ethical, safety & regulatory issues relating to clinical implementation of gene transfer technology.
The objectives are threefold:

- Fostering interaction between regulators - both at the European centralised and national levels - members of Ethics committees, companies, decision-makers, scientists, physicians and patients' groups in order to facilitate and harmonise clinical implementation of gene therapy;
- Offering a potential for a referral organisation following-up on evolving technologies to foster broad circulation of validated key-information;
- Increase public accountability and downstream public acceptance of these interventions which make use of GMOs. Euregenethy also aims at anticipating on challenging scientific issues, which will attract interest and/or raise safety, regulatory, ethical or public concerns.

In 2002 an Opinion Paper[94] on the Current Status of the Regulation of Gene Therapy in Europe was published provided a critical review of the system at the European level and in selected countries (Austria, Belgium, Denmark, France, Germany, Israel, Italy, The Netherlands, Spain, Sweden, Switzerland and United Kingdom). This review has been a valuable starting point for this project and Perseus could focus on changes occurring since the publication. Furthermore, the emphasis of this project is clearly on the GMO regulation, an aspect which is partly covered but not discussed in the opinion paper. Finally, the recommendations of the opinion paper have been taken up in different discussion and are added as appropriate in this report.

[94] O.Cohen-Hanguenauer, F.Rosenthal, B. Gänsbacher, R.Bolhuis, K. Dorsch-Häsler, Z.Eshhar, G.Gahrton, P.Hokland, C.Melani, E.Rankin; K.Thielemans, R.Vile, H.Zwierzina & K.Cichutek (2002) Opinion Paper on the Current Status of the Regulation of Gene Therapy in Europe. Human Gene Therapy 13:2085-2110

Annex 2. List of authorities contacted during this project.

The following table lists all authorities that were contacted during the project.

Country	Authority
Austria	Federal Ministry of Education, Science and Culture, Dept. BrGt
Austria	Ministry of Social Security and Generations
Belgium	FPS Health, Food Chain Safety and Environment, General direction Animals, Plants and Food, Division Human medicine, Dept. R& D
Belgium	Service of Biosafety and Biotechology (SBB), Institute of Public Health (IPH), Federal Public Service (FPS) Health, Food Chain Security and Environment
Cyprus	Environment Service, Ministry of Agriculture, Natural Resources and Environment
Cyprus	Ministry of Health
Czech Republic	Department of Environmental Risks, Ministry of the Environment
Denmark	The Danish Forest and Nature Agency
Denmark	National Working Environment Authority
Denmark	Ministry of the Environment, Danish Forest and Nature Agency, Agriculture and Biotechnology
Denmark	Danish Medicines Agency
EMEA	EMEA
Estonia	Estonian Ministry of Environment, Nature Protection Department
Estonia	Ministry of the Environment - Labour Inspection
Estonia	State Agency of Medicines
Finland	Ministry of Social Affairs and Health - Board for Gene Technology
Finland	National Agency for Medicines
France	Ministère de l'écologie et du développement durable, Bureau des Biotechnologies et des Installations agricoles et agro-alimentaires, Service de l'Environnement Industriel, Direction de la Prévention des Pollutions et des Risques
France	Agence Française de Sécurité Sanitaire des Produits de Santé; Unité Produits Biologiques à effet thérapeutique
France	Agence Française de Sécurité Sanitaire des Produits de Santé, Dept Evaluation of Biological Products
France	Agence Française de Sécurité Sanitaire des Produits de Santé; Legal service
France	Agence Fançaise de Sécurité Sanitaire des Aliments; Agence nationale du médicament vétérinaire
France	Hôpital Saint-Louis TGOM - Institut d'Hématologie
Germany	Federal Office of Consumers Protection and Food Safety, Dept. of Genetic Engineering
Germany	Paul-Ehrlich-Institut, Bundesamt für Sera und Impfstoffe / PEI
Greece	Ministry of Environment, Physical Planning and Public Works.

Country	Authority
Greece	National Organisation for Medicines (EOF), Ministry of Health & Social Solidarity Clinical Trials Section, Pharmaceutical studies and research division,
Hungary	Ministry of Agriculture and Rural Development
Hungary	Ministry of Health
Hungary	National Institute of Pharmacy
Hungary	Ministry of Environment and Water, Department of International Treaties for Nature Conservation
Iceland	Environment and Food Agency of Iceland
Ireland	EPA
Ireland	Department of Agriculture and Food
Ireland	Irish Medicines Board
Italy	Ministero dell'Ambiente e della Tutela del Territorio, Direzione per la Protezione della Natura, Divisione Biosicurezza e controllo sull'immissione nel territori di OGM
Italy	Ministero della Salute, Direzione Generale, Ufficio VI
Italy	Ministero della Salute, Agenzia Italiana del Farmaco, Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali;;
Italy	Istituto Superiore di Sanità, Dipartimento di Biologia Cellulare e Neuroscienze
Latvia	Clinical Trial Department, State Agency of Medicine
Liechtenstein	Amt für Umweltschutz
Lithuania	Ministry of Environment - Nature Protection Dpt
Lithuania	Ministry of Health
Luxembourg	Ministry of Health
Malta	Malta Environment and Planning Authority
Netherlands	RIVM / SEC / Bureau GGO
Netherlands	Ministry of Housing, Spatial Planning and the Environment
Norway	Ministry for Environment
Norway	Environmental Department of Norway, Directorate for Nature Management
Norway	Directorate for Health and Social Affairs
Poland	Sanitary Inspectorate. Dept of food, nutrition and daily use objects hygiene
Poland	Ministry of The Enviroment, Unit of GMO
Poland	Department of the Medicinal Products Policy, Ministry of Health
Portugal	Instituto do Ambiente - IA
Portugal	INFARMED National Institute of Pharmacy and Medicines
Slovac Republic	Ministry of Environment of SR, Biosafety Department
Slovac Republic	Institute of Public Health
Slovac Republic	Slovak Academy of Science
Slovac Republic	Ministry of Health Slovak Ethical Committee
Slovac Republic	State Institute for Drug Control
Slovenia	Ministry of the Environment, Spatial Planning and Energy. Environmental Dept. Sector for biotechnology
Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
Spain	Ministerio de Medio Ambiente, DG de Calidad y Evaluacion Ambiental
Spain	Subdirección General de Medicamentos de Uso Veterinario Agencia Española de Medicamentos y Productos Sanitarios

Country	Authority
Spain	División de Productos Biológicos y Biotecnología; Agencia Española de Medicamentos y Productos Sanitarios
Sweden	Medical Products Agency
Sweden	Chemistry and Microbiology Division, Swedish Work Environment Authority
Switzerland	Swiss Agency for the Environment, Forests and Landscapes; Substances, Soil and Biotechnology Division
United Kingdom	Biological Agents and GMOs Policy Section; Health and Safety Executive
United Kingdom	DEFRA, Department for Environment, Food and Rural Affairs
United Kingdom	Biological Agents and GMOs Policy Section; Health and Safety Executive

Annex 3. Listing of clinical trials performed in EU.

Data about Clinical Trials with GMOs in Europe have been collected using public information. For deliberate release applications the Joint Research Centre (JRC) website has been used (last accessed April 10, 2006):

http://biotech.jrc.it/deliberate/gmo.asp
http://gmoinfo.jrc.it/gmo_browse_geninf.asp

Also, the Clinical Trial site of "The Journal of Gene Medicine" of the European Society for Gene Therapy has been checked (referred to as "Wiley"; last updated January 2006):

http://www.abedia.com/wiley/index.html

The EUdraCT database could not be consulted.

Furthermore data from websites of the Member States were included were possible (referred to as "CA"):

http://www.biosafety.be/GT/Regulatory/Table_2.html
http://www.ogm.gouv.fr/experimentations/evaluation_scientifique/cgb/CGB_rapports_activite.htm
http://www.vrom.nl/ggo-vergunningverlening
http://www.mma.es/calid_amb/seg_bio/pdf/tablaliberaciones_marzo_2006.pdf
http://www.mma.es/calid_amb/seg_bio/pdf/Not_utilz_marzo_2006.pdf

Including a trial in this list does not necessarily mean that it was approved or conducted.
The indicative list is by the method limited because:

- Not for all trials data are publicly available;
- Due to the language some websites could not be consulted;
- Contained use class 1 trials do not always need notification;
- Limited time coverage or backlog in reporting.

Also, from the data provided it was not always possible to discriminate between pre-clinical and clinical trials; some pre-clinical trials might be wrongly included.

Sources are refered to as

- Wiley (http://www.abedia.com/wiley/index.html)
- JRC (http://gmoinfo.jrc.it/gmo_browse_geninf.asp or http://biotech.jrc.it/deliberate/gmo.asp)
- CA (relevant CA website as indicated above)

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Austria	Phase I Study of the Immunotherapy of Metastatic Malignant Melanoma by a Cancer Vaccine Consisting of Autologous Cancer Cells Transfected with the Human IL- 2 Gene	humans	Interleukin-2 (IL-2)		Univ. of Vienna Medical School Dept of Dermatology Vienna		Wiley
Austria	Transfer of Interleukin-4 and Interleukin-10 in Patients with severe Inflammatory Disease of the Rectum	humans	Interleukin-4 (IL-4) Interleukin-10 (IL-10)		University Clinics of Surgery Vienna		Wiley
Belgium	Gene therapy for the treatment of glioblastoma multiforme with in vivo tumour transduction with the herpes simplex thymidine kinase gene/ganciclovir system	humans	Herpes simplex virus thymidine kinase (HSV-TK) Neomycin resistance (NeoR)	Retrovirus	Hopital Erasme Brussels	CU	Wiley
Belgium	Prospective, open-label, parallel-group, randomised, multicenter trial comparing the efficacy of surgery, radiation, and injection of murine cells producing herpes simplex thymidine kinase vector followed by intravenous ganciclovir against the efficacy of surgery and radiation in the treatment of newly diagnosed, previously untreated gliogblastoma	humans	Herpes simplex virus thymidine kinase (HSV-TK) Neomycin resistance (NeoR)	Retrovirus	Hopital Erasme Brussels	CU	Wiley
Belgium	A phase I study in patients with recurrent or metastatic squamous cell carcinoma of the head and neck using SCH 58500 (rAd/p53) administered by single intratumoural injection	humans	p53	Adenovirus	Universitair Ziekenhuis Gasthuisberg Leuven	CU	Wiley
Belgium	A phase II gene therapy study in patients with non-small cell lung cancer using SCH58500 (rAd/p53) in combination with chemotherapy for multiple cycles	humans	p53	Adenovirus	Akademisch Ziekenhuis Vrije Universiteit Brussel Brussels	CU	Wiley
Belgium	Pilot study of immunisation with recombinant canarypox virus vCP1469A expressing the MAGE-1.A1 and MAGE-3.A1 cytolytic T lymphocytes epitopes in patients with malignant melanoma, non-small cell lung carcinoma, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma or bladder carcinoma	humans	MAGE-1.A1 MAGE-3.A1	Poxvirus	Cliniques universitaires Saint-Luc Brussels	CU	Wiley
Belgium	Phase II randomised study of immunotherapy of advanced breast cancer by repeated intramuscular injection of a recombinant vaccinia virus containing sequences coding for human MUC-1 and interleukin-2 (TG1031) comparing two doses levels	humans	MUC-1 Interleukin-2 (IL-2)	Vaccinia virus	Universitair Ziekenhuis Gasthuisberg Gent	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Belgium	A phase II, multi-center, open label, randomised study to evaluate biodistribution and transmission, effectiveness and safety of two treatment regimens of Ad5CMV-p53 administered by intra-tumoural injections in 40 evaluable patients with advanced squamous cell carcinoma of the head and neck (SCCHN)	humans	p53	Adenovirus	Hopital Erasme Brussels	CU	Wiley
Belgium	A phase II/III trial of chemotherapy alone plus SCH 58500 in newly diagnosed stage III ovarian and primary peritoneal cancer patients with >0.5cm and <2cm residual disease following surgery	humans	p53	Adenovirus	Cliniques universitaires Saint-Luc Brussels	CU	Wiley
Belgium	A phase I feasibility trial of a live, genetically modified Salmonella typhimurium bacillus (VNP20009) for the treatment of cancer by intra-tumoural injection			Salmonella typhimurium	Universitair Ziekenhuis Gasthuisberg Leuven	CU	Wiley
Belgium	A phase III open-label, comparative, multicentre trials to test the concept of durable virologic suppresion in subjects with primary HIV-1 infection after intensive induction of quadruple HAART followed by double blind randomisation to HIV vaccination with ALVAC-HIV (vCP-1452) and remune or placebo while maintaining optimal therapeutic viral suppression	humans	vCP-1452	Poxvirus	Centre hospitalier universitaire St Pierre Brussels	CU	Wiley
Belgium	Randomised, multicentre, phase II study evaluating two doses of TG4010 (MVA-MUC-1-IL-2) in patients with metastatic breast cancer	humans	MUC-1 Interleukin-2 (IL-2)	Vaccinia virus	Hopital Erasme Brussels	CU	Wiley
Belgium	Randomised, multicentre, phase II study evaluating the clinical efficacy of TG4010 (MVA-MUC-1-IL-2) in association with chemotherapy patients with non small cell lung cancer	humans	MUC-1 Interleukin-2 (IL-2)	Vaccinia virus	Hopital Erasme Brussels	CU	Wiley
Belgium	A phase III, multi centre, open-label, randomised study to compare the overall survival and safety of bi-weekly intratumoural administration of INGN 201 versus weekly methotrexate in 240 patients with refractory squamous cell carcinoma of the head and neck (SCCHN)	humans	p53	Adenovirus	Cliniques universitaires Saint-Luc Brussels	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Belgium	A phase III, multi centre, open-label, randomised study to compare the effectiveness and safety of intratumoural administration of INGN 201 in combination with chemotherapy versus chemotherapy alone in 288 patients with recurrent squamous cell carcinoma of the head and neck (SCCHN)	humans	p53	Adenovirus	Cliniques universitaires Saint-Luc Brussels	CU	Wiley
Belgium	Etude du vaccin TG4010 utilisant une suspension virale constituee d'un virus recombinant de la vaccine (MVA) vehiculant les genes codant pour l'antigene humain MUC-1 et l'interleukine-2 chez des patients atteints de cancer	humans	MUC-1 Interleukin-2 (IL-2)	Vaccinia virus	Cliniques universitaires Saint-Luc Brussels	CU	Wiley
Belgium	A phase 1 randomised, placebo controlled, double blind, dose escalation trial to evaluate the safety and immunogenicity of tgAAC009, a gag-PR-DRT AAV HIV vaccine	humans	HIV-1 Gag/Protease plus rev	Adeno-associated virus	Centre hospitalier universitaire St Pierre Brussels	CU	Wiley
Belgium	Phase I/II multicentre study of TG1024 (Adenovirus interleukin 2) in patients with metastatic melanoma or other advanced solid tumor cancers	humans	Interleukin-2 (IL-2)	Adenovirus	Hopital Erasme Brussels	CU	Wiley
Belgium	Clinical research program : Gene-therapy by the Use of a Recombinant Adenovirus in the Treatment of p53 Deficient Cancers	humans	wild-type p53 tumor suppressor gene	Human adenovirus type 5	Schering Plough NV/SA	DR	JRC
Belgium	Specific immunotherapy against MUC-1 antigen - Study TG4010.04 : "Randomised, multicenter, phase II study evaluating two doses of TG4010(MVA-MUC-1-IL-2) in patients with metastatic breast cancer", Study TG4010.05 : "Randomised, multicenter, phase II study evaluating the clinical efficacy of TG4010(MVA-MUC-1-IL-2) in association with chemotherapy in patients with non small cell lung cancer"	humans	sequences coding for the human MUC-1 antigen and IL-2	MVA	Transgene S.A.	DR	JRC
Belgium	Phase II study evaluating the clinical efficacy of TG4010(MVA-MUC-1-IL-2) in patients with metastatic renal cell carcinoma	humans	sequences coding for the human MUC-1 antigen and IL-2	MVA	Transgene S.A.	DR	JRC
Belgium	Development of a live vaccine against feline leukemia. Experiment outside containment (clinical trial) for the study of the safety of a sucutaneous administration of a recombinant canarypoxvirus expressing FELV genes.	cats	env and gag genes of the type A virus of feline leukemia (FELV)	canarypoxvirus	Merial	DR	JRC

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Belgium	Development of a combined live vaccine against feline leukemia. Experiment outside containment (clinical trial) for the study of the safety of a sucutaneous administration of a recombinant canarypoxvirus expressing FELV genes.	cats	env and gag genes of the type A virus of feline leukemia (FELV)	canarypoxvirus	Merial	DR	JRC
Belgium	Development of a combined vaccine against equine influenza and tetanus. Experiment outside containment (clinical trial) for the study of the safety and efficacy of an intramuscular administration of recombinant canarypoxvirus expressing equine influenza virus Haemagglutinin gene.	horses	haemagglutinin gene from equine influenza virus A2/Kentucky/94 or equine influenza virus A2/Newmarket/2/93	canarypoxvirus	Merial	DR	JRC
Belgium	Evaluation of efficacy of Salmonella Dublin-Typhimurium vaccine, double gene deleted avirulent live culture in calves.	calves	genetic modification of Salmonella enterica by deletion of 2 genes (ssaC and ssaT)	Salmonella Dublin and Typhimurium	Pharmacia Animal health	DR	JRC
Belgium	Phase I multicentre study of TG1024 (Adenovirus interleukin 2) in patients with metastatic melanoma or other advanced solid tumor cancers	Humans	gene coding for human interleukin 2	Human adenovirus type 5	Transgene S.A.	DR	JRC
Belgium	Evaluation of the safety of Feline Herpes Virus, bivalent deleted live vaccine, administered as intranasal vaccine to cats	Cats	gene for the env glycoprotein or gene for the gag protein of the Feline immunodeficiency virus (FIV)	Feline Herpes Virus	Pfizer, Animal Health Group	DR	JRC
Belgium	Newly diagnosed or recurrent Glioblastoma multiforme	humans	Thymidine Kinase (HSV-TK1), neomycin resistance (NeoR)	Amphotropic Murine Leukemia Virus	Sandoz Pharma, LTD	CU	CA
Belgium	Newly diagnosed previously untreated Glioblastoma	humans	Thymidine Kinase (HSV-TK1), neomycin resistance (NeoR)	Amphotropic Murine Leukemia Virus	Genetic therapy, Inc., Sandoz Pharma, Ltd	CU	CA
Belgium	Squamous cell carcinoma of the Head and Neck	humans	Wild-type p53	Human Adenovirus serotype 5	Schering Plough NV/SA	CU	CA
Belgium	Non-Small Cell Lung Cancer	humans	Wild-type p53	Human Adenovirus serotype 5	Schering Plough NV/SA	CU	CA
Belgium	Malignant melanoma, Non-Small Cell Lung Cancer, Squamous cell carcinoma of the Head and Neck, Bladder transitional cell carcinoma	humans	HLA-A1 restricted CTL epitope of MAGE-1 and MAGE-3 genes	Canarypox Virus (ALVAC)	Pasteur Mérieux Connaught	CU	CA

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Belgium	Metastatic adenocarcinoma of the Breast	humans	Muc-1 and Interleukine 2 (IL-2)	Attenuated Vaccinia Virus (Copenhagen Strain)	Transgène	CU	CA
Belgium	Recurrent squamous cell carcinoma of the Head and Neck	humans	Wild-type p53	Human Adenovirus serotype 5	Rhone-Poulenc Rorer	CU	CA
Belgium	Ovarian and primary peritoneal cancer	humans	Wild-type p53	Human Adenovirus serotype 5	Schering Plough NV/SA	CU	CA
Belgium	Non-hematologic malignancies	humans	Not relevant	Not relevant	Vion Pharmaceuticals, Inc.	CU	CA
Belgium	AIDS	humans	vCP-1452	Attenuated Canarypox Virus (ALVAC)	Sponsor of the study: Glaxo Wellcome; Manufacturer of the GMO: Aventis-Pasteur S.A.	CU	CA
Belgium	Metastatic Breast Cancer	humans	Muc-1 and Interleukine 2 (IL-2)	Attenuated Vaccinia Virus (Ankara Strain)	Transgene S.A.	CU	CA
Belgium	Non-Small Cell Lung cancer	humans	Muc-1 and Interleukine 2 (IL-2)	Attenuated Vaccinia Virus (Ankara Strain)	Transgene S.A.	CU	CA
Belgium	Refractory squamous cell carcinoma of the Head and Neck	humans	Wild-type p53	Human Adenovirus serotype 5	Introgen Therapeutics, Inc.	CU	CA
Belgium	Recurrent squamous cell carcinoma of the Head and Neck	humans	Wild-type p53	Human Adenovirus serotype 5	Introgen Therapeutics, Inc.	CU	CA
Belgium	Progressive metastatic renal cell carcinoma	humans	Muc-1 and Interleukine 2 (IL-2)	Attenuated Vaccinia Virus (Ankara Strain)	Transgene S.A.	CU	CA
Belgium	Chronic angina pectoris	humans	human FGF-4	Human Adenovirus serotype 5	Schering N.V./S.A.	CU	CA
Belgium	AIDS	humans	genes for the gag, protease and part of the reverse transcriptase proteins of HIV-1	Adeno Associated Virus serotype 2	International AIDS Vaccine Initiative (IAVI)	CU	CA

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Belgium	Metastatic melanoma or other advanced solid tumors	humans	Interleukine 2 (IL-2)	Human Adenovirus serotype 5	Transgene S.A.	CU	CA
Belgium	Operable high-grade glioma	humans	Thymidine Kinase (HSV-TK1)	Human Adenovirus serotype 5	Ark Therapeutics Ltd	CU	CA
Czech Republic	Granulocyte-macrophage colony-stimulating factor gene-modified vaccines for immuno therapy of cancer	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)		Institute of Molecular Genetics, Academy of Sciences of the Czech Republic	CU	Wiley
Denmark	A Multicenter, Randomised, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy of BIOBYPASS? (ADGVVEGF121.10NH)	humans			Cardiovascular Laboratory 2014, The Heart Center, University hospital Rigshospitalet Copenhagen	CU	Wiley
Denmark	The Effect of Mobilised Stem Cell by G-CSF and VEGF Gene Therapy in Patients With Stable Severe Angina Pectoris	humans	Vascular endothelial growth factor (VEGF)	Naked/Plasmid DNA	Cardiovascular Laboratory 2014, The Heart Center, University hospital Rigshospitalet Copenhagen	CU	Wiley
Finland	Thymidine kinase gene therapy for human malignant glioma, using replication-deficient retroviruses or adenoviruses.	humans	Herpes simplex virus thymidine kinase (HSV-TK) LacZ	Retrovirus	Univ. of Kuopio Molecular Medicine POB 1627 Kuopio	CU	Wiley
Finland	Adenovirus-mediated gene transfer to lower limb artery of patients with chronic critical leg ischemia	humans	LacZ Vascular endothelial growth factor (VEGF)	Adenovirus	Univ. of Kuopio Molecular Medicine POB 1627 Kuopio	CU	Wiley
Finland	Catheter-mediated vascular endothelial growth factor gene transfer to human coronary arteries after angioplasty.	humans	Vascular endothelial growth factor (VEGF)	Adenovirus	Univ. of Kuopio Molecular Medicine POB 1627 Kuopio	CU	Wiley
France	Aerosol administration of a recombinant adenovirus expressing CFTR to cystic fibrosis patients: a phase I clinical trial.	humans	Cystic fibrosis transmembrane conductance regulator (CFTR)	Adenovirus	CH Lyon Sud, Hop. Debrousse Unite Pneumologie Pediatrique Lyon	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
France	Gene Therapy in Advanced Cancers	humans	Interleukin-2 (IL-2)	Retrovirus	Institut Curie Dept. de biologie clinique 26 rue d'Ulm Paris	CU	Wiley
France	Treatment of Patients with Advanced Cancer Using Tumor Infiltrating Lymphocytes Transduced with the Gene of Resistance to Neomycin	humans	Neomycin resistance (NeoR)	Retrovirus	Centre Leon Berard Lab. Biologie des Tumeurs 28 rue Laennec Lyon	CU	Wiley
France	Gene Therapy in Patients with Breast Cancer	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Retrovirus	Centre Leon Berard Lab. Biologie des Tumeurs 28 rue Laennec Lyon	CU	Wiley
France	Gene Therapy of Mucopolysaccharidosis Type I (Hurlers Syndrome)	humans	Alpha-1-iduronidase (IDUA)	Retrovirus	Hospital Necker-Enfants Malades INSERM Unit 429 149 rue de Sevres Paris	CU	Wiley
France	Gene Therapy of Severe Combined Immune Deficiency Due to Adenosine Aeaminase (ADA) Deficiency	humans	Adenosine deaminase (ADA)	Retrovirus	Hospital Necker-Enfants Malades INSERM Unit 429 149 rue de Sevres Paris	CU	Wiley
France	Gene Therapy in Patients with Colon Carcinoma	humans	Interleukin-2 (IL-2)	Adenovirus	Transgene 11 rue Molsheim Strasbourg	CU	Wiley
France	Gene Therapy for Glioblastoma in Adult Patients: Safety and Efficacy Evaluation of an In Situ Injection of Recombinant Retroviruses Producing Cells Carrying the Thymidine Kinase Gene of the Herpes Simplex Type 1 Virus, to be Followed with the Administration of Ganciclovir	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Retrovirus	CERVI, Hopital Pitie-Salpetriere 83 Bd de l'Hopital Paris	CU	Wiley
France	Gene Therapy of Metastatic Malignant Melanoma: Evaluation of Tolerance of Intratumoral Injection of Cells Producing Recombinant Retrovirus Carrying the Thymidine Kinase Gene Type Herpes Simplex Virus, Followed by Administration of Ganciclovir	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Retrovirus	CERVI, Hopital Pitie-Salpetriere 83 Bd de l'Hopital Paris	CU	Wiley
France	Gene Therapy in Patients with Advanced Cancer	humans	LacZ	Retrovirus	Institut Paoli-Calmettes Centre de Thérapie Génique 232 Blvd Sainte-Marguerite Marseille	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
France	Use of donor T-lymphocytes expressing herpes-simplex thymidine kinase in allogeneic bone marrow transplantation: a phase I-II study.	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Retrovirus	Etablis. de Transfusion Sanguine de Franche-Comte Lab. d'Histocompatibilite & Therap. Immuno-moleculaire Besançon	CU	Wiley
France	Gene Therapy for lung cancer	humans	Interleukin-2 (IL-2)	Adenovirus	Institut Gustave Roussy Unite Immunotherapie +4 39 rue Camille Desmoulins Villejuif	CU	Wiley
France	Gene therapy in patients with non-small cell lung cancer	humans	LacZ	Adenovirus	Institut Gustave Roussy Unite Immunotherapie +4 39 rue Camille Desmoulins Villejuif	CU	Wiley
France	Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease	humans	Gamma c common chain receptor	Retrovirus	Hospital Necker-Enfants Malades INSERM Unit 429 149 rue de Sevres Paris	CU	Wiley
France	Neuroprotective Gene Therapy for Huntington's Disease Using a Polymer Encapsulated BHK Cell Line Engineered to Secrete Human CNTF	humans	Ciliary neurotrophic factor (CNTF)		INSERM U421 Créteil	CU	Wiley
France	Gene Therapy for lung cancer	humans	Ad.RSV betagal	Adenovirus	Institut Gustave Roussy Unite Immunotherapie +4 39 rue Camille Desmoulins Villejuif	CU	Wiley
France	Gene therapy for Duchenne/Becker muscular dystrophy	humans	Dystrophin	Naked/Plasmid DNA	Institut de Myologie, AFM, Batiment Babinski, Hopital de la Salpetriere, 75651 Paris Cedex 136 Paris	CU	Wiley
France	Gene therapy with Adv-IL-2 in unresectable digestive cancer: phase I-II study	humans	Interleukin-2 (IL-2)	Adenovirus	Surgical Department Centre Hospitalo-Universitaire Lyon Sud Lyon	CU	Wiley
France	Memory cytotoxic T lymphocyte responses in human immunodeficiency virus type 1 (HIV-1)-negative volunteers immunised with a recombinant canarypox expressing gp160 of HIV-1 and boosted with a recombinant gp160	humans	HIV-1 Env	Poxvirus	Unite de Virologie et Immunologie cellulaire Institut Pasteur Paris	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
France	Etude de phase II, randomisée, contrôlée contre placebo, évaluant l'immunogénicité et l'innocuité d'une stratégie d'immunisation comparant deux schémas de vaccination suivi d'un rappel homologue avec ALVACHIV (vcp 1452) chez des sujets infectés par le VIH	humans			ORVACS	CU	CA
France	Essai multicentrique de phase II, en ouvert, évaluant, l'efficacité du TG4001 (MVA-HPV-IL2) chez des patientes présentant une méoplasie intra-épithéliale du col de l'utérus de grade 2/3 (CIN2/3) liée à l'infection par l'HPV16 (protocole TG4001.07) en 2004-2005	humans			TRANSGENE SA	CU	CA
France	Essai de phase I/II d'un traitement biologique par administrations intra-tumorales de TG1042 (adénovirus-interféron-y) chez des patients présentant un lymphome cutané à cellules T (CTCL) à un stade avancé ou un lymphome cutané à cellules B (CBCL) à localisations multiples	humans			TRANSGENE SA	CU	CA
France	Essai de phase I de l'administration intratumorale et péritumorale d'une dose fixe d'ADN nu codant pour le gène de la _-galactosidase et d'une modalité unique d'électrotransfert tumoral et péritumoral dans les localisations cutanées des tumeurs malignes	humans			Institut Gustave-Roussy	CU	CA
France	Traitement des formes cérébrales d'adrénoleucodystrophie liée à l'X (ALD) de l'enfant par transfert ex vivo du gène ALD dans les cellules CD34+ autologues				INSERM	CU	CA
France	A controlled, randomise, parallel group, multicentre study of the efficacy and safety of Herpes Simplex Virus – thymidine kinase gene therapy (Cerepro) with subsequent ganciclovir, for the treatment of patients with operable high grade malignant glioma	humans			ARK THERAPEUTICS	CU	CA
France	A comparative double-blind placebo-controlled study of immunogenicity and safety of two doses 10^5 and 10^7 of SC599 oral vaccine, a Live attenuated Shigella dysenteria 1 vaccine strain in healthy human adult volunteers.	humans			Institut Pasteur	CU	CA

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
France	Etude de phase II, randomisée, contrôlée contre placebo, évaluant l'immunogénicité et l'innocuité d'une stratégie d'immunisation comparant deux schémas de vaccination suivi d'un rappel homologue avec ALVACHIV (vcp 1452) chez des sujets infectés par le VIH	humans			ORVACS	CU	CA
France	Etude randomisée contre placebo de thérapie génique intra-myocardique par un facteur de croissance stimulant l'angiogénèse (VEGF) chez les patients présentant un myocarde ischémique incomplètement revascularisable	humans			CHU DE BORDEAUX	CU	CA
France	Etude de phase II, randomisée, en double insu, en groupe parallèles, évaluant l'efficacité et la tolérance NV1FGF versus placébo, chez des patients atteints d'occlusion sévère des artères périphériques	humans			AVENTIS	CU	CA
France	Essai de phase II d'évaluation d'efficacité du TG4010 (MVA-HPV- IL2 chez des patients atteints d'un cancer du rein métastasique	humans			TRANSGENE SA	CU	CA
France	Etude de phase I, en dose unique, en escalade de doses, du vecteur MaxAdFVIII chez des patients atteints d'hémophilie A	humans			GENSTAR	CU	CA
France	Etude de tolérance et d'efficacité en double insu, randomisée, contrôlée versus placebo d'une thérapie par transfert du gène humain FGF-4 porté par un adénovirus Ad5.1, administrée à doses croissantes, par voie intramusculaire sur une journée, chez des patients souffrant d'une artériopathie oblitérante périphérique chronique sans autre alternative qu'une amputation				SCHERING S.A	CU	CA
France	Essai visant au traitement des maladies auto-immunes, compliquées d'une myelodyspasie / leucémie secondaire, par allogreffe géno-identique de cellules souches hématopoïétiques et de lymphocytes T génétiquement modifiés du donneur exprimant le gène HSV-TK.		HSV-TK gene		ARDIVI	CU	CA
France	assessment of efficacy, assessment of safety			Canarypoxvirus	Merial SAS	DR	JRC
France	assessment of efficacy, assessment of safety			Canarypoxvirus	Rhône-Mérieux Laboratory	DR	JRC
France	assessment of safety, Pseudorabies vaccine				Bayer Pharma Santé Animale	DR	JRC
France	assessment of safety, Pseudorabies vaccine				Rhône-Mérieux	DR	JRC

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
France	Development of a vaccine against feline rabies. Experiment outside containment (clinical trial) for the study of the safety and the efficacy of a subcutaneous administration of a recombinant canarypoxvirus expressing the surface glycoprotein G gene from Rabies virus (vCP65).	cats	surface glycoprotein G gene from Rabies virus (vCP65)	Canarypoxvirus	Merial Laboratoires	DR	JRC
Germany	Gene Therapy in Patients with Myeloma	humans	Neomycin resistance (NeoR)	Retrovirus	Free University of Berlin Rudolf Virchow University Clinic Berlin		Wiley
Germany	Gene Therapy in Patients with Melanoma	humans	Interleukin-2 (IL-2) Granulocyte-macrophage colony stimulating factor (GM-CSF)	Lipofection	University Medical Centre Freiburg Dept. of Medicine I (Haematology/Oncology) Freiburg		Wiley
Germany	Phase-I immunotherapy study of B7.1 and IL-2-expressing allogeneic tumor cells as a vaccine in patients with progressive renal-cell carcinoma	humans	Interleukin-2 (IL-2) HLA-B7	Lipofection	University Medical Centre Freiburg Dept. of Medicine I (Haematology/Oncology) Freiburg		Wiley
Germany	Induction of tumor-specific cytotoxic T lymphocytes by immunisation with autologous tumor cells and interleukin-2 gene transfected fibroblasts.	humans	Interleukin-2 (IL-2)	Lipofection	University Medical Centre Freiburg Dept. of Medicine I (Haematology/Oncology) Freiburg		Wiley
Germany	Gene Therapy in Patients with Melanoma	humans	Interleukin-7 (IL-7) Interleukin-12 (IL-12) Granulocyte-macrophage colony stimulating factor (GM-CSF)	Gene gun	DKFZ/Klinikum Mannheim Dermato-Onkologie, Haus 24 Theodor Kutzer Ufer 1 Mannheim		Wiley
Germany	Gene Therapy in Patients with Melanoma	humans	Interleukin-7 (IL-7) Interleukin-12 (IL-12) Granulocyte-macrophage colony stimulating factor (GM-CSF)	Gene gun	DKFZ/Klinikum Mannheim Dermato-Onkologie, Haus 24 Theodor Kutzer Ufer 1 Mannheim		Wiley
Germany	Interleukin- 7 Gene Transfer in Patients with Metastatic Colon Carcinoma, Renal Cell Carcinoma, Melanoma or Lymphoma	humans	Interleukin-7 (IL-7) Interleukin-2 (IL-2)	Naked/Plasmid DNA	Rheinische Friedrich-Wilhelms Univ. Division of Oncology and Hematology Med Univ Klinik und Poliklinik		Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
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Germany	Vaccination with IL-12 gene-modified autologous melanoma cells: preclinical results and a first clinical phase I study	humans	Interleukin-7 (IL-7) Interleukin-12 (IL-12) Granulocyte-macrophage colony stimulating factor (GM-CSF)	Gene gun	DKFZ/Klinikum Mannheim Dermato-Onkologie, Haus 24 Theodor Kutzer Ufer 1 Mannheim		Wiley
Germany	Cell therapy using microencapsulated 293 cells transfected with a gene construct expressing CYP2B1, an ifosfamide converting enzyme, instilled intra-arterially in patients with advanced-stage pancreatic carcinoma: a phase I/II study	humans	Cytochrome p450	Naked/Plasmid DNA	Universität Heidelberg Sektion Molekulare Gastroenterologie Med. Klinik IV Theodor Kutzer Ufer Mannheim		Wiley
Germany	Phase I Trial for Primary Untreated Head and Neck Squamous Cell Cancer (HNSCC) UICC Stage II-IV with a Single Intratumoral Injection of hIL2 Plasmids Formulated in DOTMA/Chol	humans	Interleukin-2 (IL-2)	Naked/Plasmid DNA	Klinikum Grosshadem Ludwig Maximilians University		Wiley
Germany	Imaging-guided convection-enhanced delivery and gene therapy of glioblastoma	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Lipofection	Department of Stereotaxy and Functional Neurosurgery University of Koln		Wiley
Germany	Adenovirus-mediated thymidine kinase gene therapy for recurrent ovarian cancer	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Adenovirus	Department of Obstetrics and Gynecology University Medical Center Hugstetter Strasse 55 Freiburg		Wiley
Germany	A Phase I Study in Patients with Invasive Bladder Cancer Using SCH 58500 (rAd/p53) Administered by Single Intratumoral Injection or by Single Intravesical Instillation	humans	p53	Adenovirus	III. Medizinische Klinik und Poliklinik, Klinikum der Johannes Gutenberg-Universität Langenbeckstrasse 1 Mainz		Wiley
Germany	Gene therapy for human malignant glioma	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Retrovirus	Department of Neurosurgery Heinrich-Heine-University Dusseldorf		Wiley
Germany	A phase II Gene therapy study in patients with non-small cell lung cancer using SCH 58500 (rAd/p53) in combination with chemotherapy for multiple cycles	humans	p53	Adenovirus	III. Medizinische Klinik und Poliklinik, Klinikum der Johannes Gutenberg-Universität Langenbeckstrasse 1		Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
					Mainz		
Germany	A Phase I Study in Patients with Non-Small Cell Lung Cancer Using SCH 58500 (rAd/p53) Administered by Single Intratumoral Injection	humans	p53	Adenovirus	III. Medizinische Klinik und Poliklinik, Klinikum der Johannes Gutenberg-Universität Langenbeckstrasse 1 Mainz		Wiley
Germany	Gene therapy in patients with glioblastoma	humans		Retrovirus			Wiley
Germany	Induction and regulation of a graft-versus-leucemia-effects after allogeneic T-cell depleted stem cell transplantation in patients with chronic myeloic leucemia (CML) and acute leucemia in complete remission by HSV-Tk (Herpes simplex virus thymidin kinase) transduced allogeneic lymphocytes and Ganciclovir-therapy in high-grade GvH (Graft versus Host) disease	humans	Herpes simplex virus thymidine kinase (HSV-TK) deltaLNGFR	Retrovirus	Medizinische Hochschule Hannover, Abteilung Hämatologie/Onkologie, Mildreed Scheel Transplantationsstation Carl Neubergstr. 1 Hannover		Wiley
Germany	Gene therapy in patients with renal cell carcinoma	humans		Naked/Plasmid DNA			Wiley
Germany	Monocentric, single-blinded,placebo-controlled Trial of increasing doses to investigate safety and tolerability of a single intratumoral injection of hIL-2-plasmid in patients with primary, untreated head- and neck-squamous cell carcinoma (HNSCC), TNM-stage II-IV	humans	Interleukin-2 (IL-2)	Naked/Plasmid DNA	Universitätsklinikum Schleswig-Holstein		Wiley
Germany	Gene therapy in patients with brain cancer	humans		Retrovirus			Wiley
Germany	A phase II, Multi-Center, Open Label, Randomised Study to Evaluate Effectiveness and Safety of Two treatment Regimens of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 78 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)	humans	p53	Adenovirus	Universtiäts-Hals-Nasen-Ohren-Klinik Im Neuenheimer Feld 400 Heidelberg		Wiley
Germany	Cytokine-Gene therapy in patients with prostate carcinoma	humans	Interleukin-2 (IL-2) Interferon-gamma (IFN-g)	Retrovirus	Institut für Experimentelle Onkologie und Therapieforschung, Klinikum r. d. Isar der TU München Ismaninger Str. 22 , Munich		Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Germany	Vaccination with autologe-mucinen-CDNA (MUC1) - transfected dendritic cells in patients with breastcancer or pancreas carcinoma.	humans		Naked/Plasmid DNA	Medizinische Klinik mit Schwerpunkt, Onkologie und Hämatologie, Charité Campus Mitte Schumannstr. 20/21 , Berlin		Wiley
Germany	Microencapsulated CYP2B1-transfected cell-mediated treatment of advanced inoperable pancreatic carcinoma, a phase -II clinical trial	humans	Cytochrome p450	Naked/Plasmid DNA	Universitätsklinikum Mannheim, II. Medizinische Universitätsklinik, Sektion Molekulare Gastroenterologie Theodor-Kutzer-Ufer 1-3 Mannheim		Wiley
Germany	An open-label, multicenter, controlled, combined parallel group and dose-escalation (0; 0,12; 1,2; 12,0 µg IL-2/10E8 cells/24 hours) study, to evaluate the safety and tolerability of an allogenetic tumor vaccine BIWB 2 containing melanoma cells transfected with the human IL-2 gene in patients with advanced malignant melanoma	humans	Interleukin-2 (IL-2)	Adenovirus	Firma Boehringer Ingelheim Pharma KG Birkendorfer Strasse 65 Biberach/Riß		Wiley
Germany	Gene therapy in patients with breast cancer	humans		Retrovirus			Wiley
Germany	Gene therapy in patients with leukemia	humans		Retrovirus			Wiley
Germany	A pilot vaccination study with wild type p53 in patients suffering from advanced malignancy using SCH 58500 (rAd/p53) administered by two subcutaneous injections	humans	p53	Adenovirus	III. Medizinische Klinik und Poliklinik, Klinikum der Johannes Gutenberg-Universität Langenbeckstrasse 1, Mainz		Wiley
Germany	Therapeutic Vaccination against Metastatic Carcinoma by Expression-modulated and Immunomodified autologous Tumor Cells: a first Clinical Phase I/II Trial	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Naked/Plasmid DNA	Medizinische Universitätsklinik und Poliklinik I Sigmund-Freud-Strasse 25, Bonn		Wiley
Germany	A Phase II/III trial of chemotherapy alone versus chemotherapy plus SCH 58500 in newly diagnosed stage III ovarian and primary peritoneal cancer patients with <= 2 cm residual disease (0-2 cm) following surgery	humans	p53	Adenovirus	Universitäts-Frauenklinik, Frauenheilkunde und Geburtshilfe Hugstetter Str. 55 Freiburg		Wiley
Germany	Phase II Randomised study of non-specific immunotherapy of malignant mesothelioma by repeated intratumoral injection of a vero cell producing human IL-2 comparing two dose levels	humans	Interleukin-2 (IL-2)	Naked/Plasmid DNA	Universitätsklinik Freiburg Hugstetter Str. 55 Freiburg		Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Germany	Phase II Study in patients with inoperable pancreatic cancer to evaluate response rate and clinical benefit of a cell therapy with encapsulated cells synthesising cytochrome P450 CYP2B1 enzyme wich concerts ifosfamide to ist active metabolites	humans	Cytochrome p450	Naked/Plasmid DNA	II. Medizinische Klinik, Fakultät für Klinische Medizin Mannheim, Universität Heidelberg Theodor Kutzer Ufer 1-3 Manheim		Wiley
Germany	The use of gene-modified donor T-cells in allogeneic bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT)	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Retrovirus	Universitätsklinikum Hamburg-Eppendorf, Einrichtung für Knochenmarktransplantation Martinistraße 52, Hamburg		Wiley
Germany	Phase I gene therapy of chronic granulomatous disease	humans	gp91phox LNGFR	Retrovirus	Klinikum der Johann Wolfgang Goethe-Universität, Medizinische Klinik III, Hämatologie/Onkologie, Theodor-Stern-Kai , Frankfurt		Wiley
Germany	Phase I-II Trial : Induction of a systemic specific immune response against specific tumor antigens after vaccination with a genetic modified HLA.A2+ breast cancer cell line	humans	HER-2/neu	Naked/Plasmid DNA	Universitätsfrauenklinik Tübingen Calwerstr. 7 Tübingen		Wiley
Germany	A Phase III, Multi-Center, open-label, randomised study to compare the Overall Survival and Safety of Bi-weekly intratumoral administration of INGN-201 versus weekly Methotrexate in 240 patients with chemotherapy refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN) - INGN-201 Trial 301	humans	p53	Adenovirus	Zentrum für Innere Medizin, Medizinische Klinik II-Ontologie/Hämatologie, Universitätsklinik Hamburg-Eppendorf Martinistrasse 52 Hamburg		Wiley
Germany	Gene therapy in patients with glioblastoma	humans		Herpes simplex virus			Wiley
Germany	Phase I study of a gene modified, B7/IL-7 transfected allogeneic tumor cell vaccine for teh treatment of metastatic renal cell carcinoma	humans	Interleukin-7 (IL-7) B7.1 (CD80)	Naked/Plasmid DNA	Medizinische Klinik f.. Hämatologie, Onkologie Charité, Campus Virchow Augustenburger Platz 1, Berlin		Wiley
Germany	Gene therapy in patients with HIV infection	humans					Wiley
Germany	Phase I vaccination study on safety and tolerability of a recombiant MVA vaccine expressing the HIV-1 nef-gene (MVA-Nef) in HIV-infected patients	humans	HIV-1 nef	Vaccinia virus	Medizinische Klinik III, Universitätsklinikum Erlangen Krankenhausstr. 12, Erlangen		Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Germany	Phase I study on safety and tolerability of a recombinant MVA vaccine expressing the HIV-1 nef-gene (MVA-Nef) administered by three subcutaneous injections to patients with asymptomatic HIV-Infection	humans	HIV-1 nef	Vaccinia virus	Infektionsambulanz und Tagesklinik, Medizinische Poliklinik der Ludwig-Maximilians-Universität Pettenkoferstrasse 8a, München		Wiley
Germany	A Phase I Randomised, Placebo-Controlled, Double-Blind Dose-Escalation Trial to Evaluate the Safety and Immunogenicity of tgAAC09, a gag-PR-DeltaRT AAV HIV Vaccine	humans		Adeno-associated virus	Zentrum Innere Medizin, Medizinische Klinik I, Universitätsklinikum Eppendorf Martinistrasse 52, Hamburg		Wiley
Germany	Gene therapy in patients with HIV infection	humans					Wiley
Germany	Monogenic diseases	humans					Wiley
Germany	REGENT I (Extension), Restenosis Gene Therapy Trial - Phase I Study	humans	NO synthase	Naked/Plasmid DNA	Klinikum der Johann-Wolfgang-Goethe-Universität Frankfurt, Med. Klinik IV, Kardiologie Theodor-Stern-Kai 7, Frankfurt		Wiley
Germany	Angiogene Gentherapie mit Ad5.1FGF-4 bei Peripherer Arterieller Verschlusskrankheit (PAVK). a) Phase I/II Study 302860. b) Phase I/II Study 303922. c) Phase I/II Study 302861. d) Phase I/II Study 303280	humans	Fibroblast growth factor (FGF)	Adenovirus	Evangelisches Krankenhaus Königin Elisabeth Herzberge; Gefäßzentrum Lichtenberg Herzbergstrasse 79, Berlin		Wiley
Germany	A phase I, randomised, double-blind, placebo controlled, escalating dose, multicenter study of Ad2/Hypoxia inducible factor (HIF)-1alpha/VP16 Gene transfer administrated by intramyocardial injection during coronary artery bypass grafting (CABG) surgery in patients with incomplete revascularisation	humans	Hypoxia inducible factor (HIF)-1ahpha/VP16	Adenovirus	Deutsches Herzzentrum Berlin Augustenburger Platz 1 Berlin		Wiley
Germany	Gene therapy in patients with coronary heart disease	humans	Fibroblast growth factor (FGF)	Naked/Plasmid DNA	Klinikum Karlsbad-Langensteinbach Guttmannstr. 1 , Karlsbad		Wiley
Germany	A phase II, randomised, double-blind, placebo-controlled parallel group, efficacy and safety study of NV1FGF in patients with severe peripheral artery occlusive disease.	humans	LacZ	Naked/Plasmid DNA	Klinik für Chirurgie und Chirurgische Onkologie, Universitätsklinikum Charité, Campus Berlin-Buch, Robert-Rössle-Klinik im HELIOS Klinikum Berlin		Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Germany	Phase I Study : non-viral gene transfer jet injection of reporter gene lac-Z in regionally advanced and metastatic or recurrent rectum carcinoma or in breast cancer skin metastases or scar relapse	humans	LacZ	Naked/Plasmid DNA	Klinik für Chirurgie und Chirurgische Onkologie, Universitätsklinikum Charité, Campus Berlin-Buch, Robert-Rössle-Klinik im HELIOS Klinikum Berlin		Wiley
Germany	Gene marking	humans					Wiley
Germany	Gene marking	humans					Wiley
Germany	Autologous transplantation of genetically modified peripheral blood stem cells after high-dose chemotherapy in patients with CML in chronic phase	humans	Neomycin-phopshotransferase	Retrovirus	Medizinische Uniklinik Freiburg, Abteilung Hämatologie / Onkologie Hugstetterstr. 55, Freiburg		Wiley
Germany	Gene therapy in patients with rheumatoid arthritis	humans		Retrovirus			Wiley
Germany	Phase IIb/III clinical study for Ad5FGF-4	humans	Fibroblast growth factor (FGF) 4	Adenovirus	Schering AG; Berlin		Wiley
Germany	A phase I study in patients with peritoneal carcinomatosis using SCH 58500 (rAd/p532) administered by single intraperitoneal instillation	humans	p53	Adenovirus	Universitäts-Frauenklinik Ulm, Universitätsfrauenklinik Freiburg Hugstetter Str. 55 Freiburg		Wiley
Germany	A Phase II Gene Therapy Study in Patients with Non-Small Cell Lung Cancer Using SCH 58500 (rAd/p53) in Combination with Chemotherapy for Multiple Cycles	humans	p54	Adenovirus	III. Medizinische Klinik und Poliklinik, Klinikum der Johannes Gutenberg-Universität Langenbeckstrasse 1, Mainz		Wiley
Germany	A phase I vaccination study with tyrosinase in patients with stage II melanoma using recombinant modified vaccinia Ankara (MVA-hTyr) administered by three subcutaneous and intradermal injections	humans	Tyrosinase	Poxvirus	III. Medizinische Klinik und Poliklinik, Klinikum der Johannes Gutenberg-Universität Langenbeckstrasse 1, Mainz		Wiley
Germany	A phase I/II study in patients with pancreatic cancer using SCH 58500 (rAd/p53) administered by multiple locoregional arterial injection in combination with chemotherapy	humans	p53	Adenovirus	Medizinische Klinik I des Universitätsklinikums Dresden Fetscherstrasse 74 , Dresden		Wiley
Germany	A multi-center study of the safety, tolerability, and clinical efficacy of multiple intratumoral injections of IL-2 gene medicine given in combination with standard chemotherapy in patients with recurrent or refractory squamous cell carcinoma of the head and	humans	Interleukin-2 (IL-2)	Naked/Plasmid DNA	Universitätsklinikum Schleswig-Holstein atzeburger Allee 160 Lübeck		Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
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Germany	Phase I study of recombinant vaccinia NY-ESO-1 (rV-NY-ESO-1) and recombinant fowlpox NY-ESO-1 (rF-NY-ESO-1) in patients with NY-ESO-1 or LAGE positive cancers and undetectable NY-ESO-1 specific serum antibodies	humans	NY-ESO-1	Poxvirus	Krankenhaus Nordwest; 2. Medizinische Klinik Steinbacher Hohl 2-26 Frankfurt am Main		Wiley
Germany	Tumor vaccination of muRas-oligopeptide transfected, autologous EBV-lymphoblasts in patients with pancreas carcinoma	humans	ligonukleotid des mutierten Ras-Onkogens, kodierend für die Aminosäuresequenz 5-21	Naked/Plasmid DNA	Direktor Medizinische Klinik I, Universität des Saarlandes Kirrbergerstr. Homburg/Saar		Wiley
Germany	phase I, open, sequential, vaccination study on safety and tolerability of different doses of a recombinant MVA HIV polytope vaccine (MVA-mBN32) in HIV negative 18-50 year old healthy volunteers	humans	Multiple genes	Vaccinia virus	Focus CDD GmbH Stresemannallee 6 Neuss		Wiley
Germany	A single blind, randomised, controlled, phase I/II vaccination study on safety and immunogenicity of a recombinant MVA-HIV polytype vaccine (MVA-mBN32) in HIV-1 infected patients with CD4 counts > 250/µl	humans	HIV genes	Vaccinia virus	Charite, Campus Virchow Kinikum Augustenburger Platz 1 Berlin		Wiley
Germany	A single blind, randomised, controlled phase II study to evaluate immunogenicity and safety of two doses of the MVA-BN nef HIV vaccibne in HIV-1 infected patients with CD4 > 250/µl	humans	HIV clade B	Vaccinia virus	Friedrich-Alexander-Universitat Erlangen-Nurnberg, Medizinische Klinik III Krankenhausstrasse 12, Erlangen		Wiley
Germany	The use of autologous gene-modified T-cells for treatment of HIV infection	humans		Retrovirus	Zentrum fur Innere Medizin, Medizinische Klinik I, Universitatsklinik Eppendorf, Martinist. 52, Hamburg		Wiley
Germany	Phase I vaccination study on safety and tolerability of a recombinant MVA vaccine expressing the HIV-1 nef-gene (MVA-Nef) in HIV-1-negative volunteers	humans	HIV-1 nef	Vaccinia virus	Medzinische Klinik III, Universitatsklinikum Erlangen Krankenhausstrasse 12, Erlangen		Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Germany	I. Virus-/Gentherapie maligner Gehirntumore mittels des rekombinanten Herpes Simplex Virus type 1 Vektors 1716 (HSV-1 ICP34.5 Mutante); II. Nicht invasive bildliche Darstellung der durch 1716 vermittelten Gentransduktion und Uberwachung der lokalen 1716 Vektor replikation mittels Positronen-Emissions-Tomographie (PET)	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Herpes simplex virus	MPI fur Neurologische Forschung und Neurologische Universitatsklinik Koln Gleuelerstrasse 50 Koln		Wiley
Germany	Phase I study on safety and tolerability of a recombinant MVA vaccine expressing the HIV-1 nef gene (MVA-Nef) in HIV-infected patients	humans	HIV-1 nef	Poxvirus	Infektionsambulanz und tagesklinik, Medzinische Poliklinik der Ludwig-Maximilians-Universitat Pettenkoferstrasse 8a, Munchen		Wiley
Germany	Phase I/II clinical trial of biologic therapy with intratumoral TG1042 (adenovirus-Interferon-Gamma) in patients with advanced cutaneous T-Cell lymphomas (CTCL)- Mycosis Fungoides and other CTCL-and multilesional cutaneous B-Cell lymphomas (CBCL)	humans	Interferon-gamma (IFN-g)	Adenovirus	Von-Esmard-Strasse 58 Munster		Wiley
Germany	A Phase III, multi-center, open-label, randomised study to compare the Effectiveness and Safety of intratumoral administration of INGN-201 in combination with chemotherapy versus chemotherapy alone in 288 patients with recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN) - INGN-201 Trial 302	humans	p53	Adenovirus	Universitätsklinik Heidelberg Im Neuenheimer Feld 400 Heidelberg		Wiley
Germany	Phase I/II clinical trial of biologic therapy with intratumoral TG1042 (Adenovirus-Interferon-gamma) in patients with Advanced Cutaneous T-Cell Lymphomas (CTCL) - Mycosis Fungoides and other CTCL - and multilesional Cutaneous B-Cell Lymphomas (CBCL)	humans	Interferon-gamma (IFN-g)	Adenovirus	Hautklinik der Universität Münster von-Esmarch-Strasse 58 Münster		Wiley
Germany	Phase I study to determine the optimum dose and dosing regimen and to assess the efficacy of a poly-epito pharmaccine (therapeutic vaccine), involving PSG2.Mel3 and MVA.Mel3, in patients with Stage III or stage IV metastatic melanoma	humans	pSG2.Mel3 MVA.Mel3	Poxvirus	Klinikum B. Franklin Hindenburgdamm 30 Berlin		Wiley
Ireland	angina pectoris	human		Human adenovirus type 5	Schering Health Care Ltd.	DR	JRC

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Italy	Treatment of Patients with Severe Combined Immunodeficiency Due to Adenosine Deaminase (ADA) Deficiency by Autologous Transplantation of Genetically Modified T Cells	humans	Adenosine deaminase (ADA) Neomycin resistance (NeoR)	Retrovirus	Istituto Scientifico HS Raffaelle Milan	CU	Wiley
Italy	Gene Transfer into Peripheral Blood Lymphocytes for In Vivo Immunomodulation of Donor Anti-Tumor Immunity in Patients Affected by Recurrent Disease After Allogeneic BMT	humans	Herpes simplex virus thymidine kinase (HSV-TK) deltaLNGFR Neomycin resistance (NeoR)	Retrovirus	Istituto Scientifico HS Raffaelle Milan	CU	Wiley
Italy	Gene Transfer into Peripheral Blood Lymphocytes for In Vitro Immunosection and In Vivo Immunomodulation of Donor Anti-Tumor Immunity in Patients Affected by EBV-induced LPD Following Allogeneic BMT	humans	Herpes simplex virus thymidine kinase (HSV-TK) deltaLNGFR Neomycin resistance (NeoR)	Retrovirus	Istituto Scientifico HS Raffaelle Milan	CU	Wiley
Italy	Active Immunisation of Metastatic Melanoma Patients with Interleukin-4 Transfected, Allogeneic Melanoma Cells. A Phase I?II Study	humans	Interleukin-4 (IL-4)	Retrovirus	Istituto Tumori, National Cancer Inst. Via G. Venezian, 1 Milano	CU	Wiley
Italy	Gene Therapy for metastatic melanoma	humans	Interleukin-2 (IL-2)	Retrovirus	Istituto Tumori, National Cancer Inst. Via G. Venezian, 1,Milano	CU	Wiley
Italy	Gene Therapy in Patients with Lymphoma and Leukemia	humans		Naked/Plasmid DNA	Istituto Medicina Sperimentale, CNR Rome	CU	Wiley
Italy	Active Immunisation of Metastatic Melanoma Patients with Interleukin- 4 Transduced, Allogeneic Melanoma Cells. A Phase I? II Study	humans	Interleukin-4 (IL-4)	Retrovirus	Istituto Tumori, National Cancer Inst. Oncologia Sperimentale D Via G. Venezian, 1 Milano	CU	Wiley
Italy	Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloblative conditionining	humans	Adenosine deaminase (ADA)		San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), Milan	CU	Wiley
Italy	Gene therapy in patients with melanoma	humans	Interleukin-4 (IL-4) Interleukin-2 (IL-2)		Cancer Bioimmuno therapy Unit and Division of Anesthesia Centro di Riferimento Oncologico Istituto di Ricovero e Cura a Carattere Scientifico Via Pedemontana Occ.le, 12 Aviano	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Italy	Active immunisation of metastatic melanoma patients with IL-2 or IL-4 gene transfected, allogeneic melanoma cells	humans	Interleukin-2 (IL-2) Interleukin-4 (IL-4)		National Cancer Institute Milan	CU	Wiley
Italy	A phase I-II study of active vaccination with autologous T-lymphocytes transduced with HSV-TK and MAGE-A3 in patients with metastatic melanoma and expression of MAGE-A3	humans	Herpes simplex virus thymidine kinase (HSV-TK) MAGE-3	Retrovirus	Istituto Tumori, National Cancer Inst. Unit of Immunotherapy of Human Tumors Via G. Venezian, 1, Milan	CU	Wiley
Italy	A Phase I Study to Evaluate the Safety/Tolerability and Immunogenicity of V-930 in Patients with Cancers Expressing HER-2 and/or CEA	humans	HER-2/CEA fusion gene	Naked/Plasmid DNA	Istituto Tumori, National Cancer Inst. Unit of Immunotherapy of Human Tumors Via G. Venezian, 1; Milan	CU	Wiley
Italy	Pilot study of transfer of the FHIT gene into bronchial non-small cell lung cancers	humans	FHIT, Tumor suppressor	Adenovirus	Istituto Tumori, National Cancer Inst. Unit of Immunotherapy of Human Tumors Via G. Venezian, 1; Mlilan	CU	Wiley
The Netherlands	Bone marrow gene transfer in three patients with adenosine deaminase deficiency	humans	Multi-Drug Resistance-1 (MDR-1)	Retrovirus	Medical Faculty, Leiden University Dept. of Molecular Cell Biology Leiden	CU	Wiley
The Netherlands	Gene Therapy in Patients with Glioblastoma	humans	Interleukin-2 (IL-2)		Academic Hospital Groningen Department of Internal Oncology Hanzeplein 1, Groningen	CU	Wiley
The Netherlands	Vaccination of melanoma patients with an allogeneic, genetically modified interleulin-2 producing melanoma cell line	humans	Interleukin-2 (IL-2)		Leiden Univ. Medical Center Department of Clinical Oncology P.O. Box 9600 (K1-P); Leiden	CU	Wiley
The Netherlands	Gene Therapy in Patients with Melanoma	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Retrovirus	Ninawell Hospital Med School Dept Cancer Med Dundee , DD1 9SY Scotland, United Kingdom	CU	Wiley
The Netherlands	Gene Therapy in patients with metastatic cancer	humans	Multi-Drug Resistance-1 (MDR-1)	Retrovirus	Introgene BV P.O. Box 2048, LEIDEN	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
The Netherlands	Treatment of Patients with Severe Combined Immunodeficiency due to Adenosine Deaminase (ADA) Deficiency by Autologous Transplantation of Genetically Modified Bone Marrow Cells	humans	Adenosine deaminase (ADA)	Retrovirus	Introgene BV P.O. Box 2048 LEIDEN	CU	Wiley
The Netherlands	Gene therapy for colorectal cancer	humans	p53	Poxvirus	Department of Immunohematology and Blood transfusion, Leiden University Medical Center, Leiden	CU	Wiley
The Netherlands	tumor vaccine based on autologous tumor cells transduced with recombinant semliki forest virus to secrete gm-csf	humans	GM-CSF	Semiliki Forest Virus	Academisch Ziekenhuis Groningen	DR	CA
The Netherlands	a multicenter, open dose escalation study to investigate the safety and tolerability of an autologous tumor vaccine in advanced melanoma	humans	GM-CSF	adeno associated virus	Erasmus MC	DR	CA
The Netherlands	evaluation of the safety of a bivalent gene deleted live vaccine of feline herpes virus, administered as an intranasal vaccination to cats	cats	FIV-env, envelop eiwit FIV-gag, core eiwit	Feline Herpes Virus	Pfizer	DR	CA
The Netherlands	(Voortzetting van) Het in de handel brengen van levende virus vaccins tegen de ziekte van Aujeszky bij varkens, die een genetisch gemodificeerde virsustam bevatten (Begonia of DM783).	pigs		Aujeszkyvirus	Intervet International	DR	CA
The Netherlands	Verzoek om vrijstelling te verkrijgen conform art.2 lid 2 d. Besluit gemodificeerde organismen voor een levend virusvaccin tegen de ziekte van Aujeszky bij varkens, dat een genetisch gemodificeerd virusstam bevat, nl. NIA3-783	pigs		Aujeszkyvirus	Fort Dodge Animal Health Holland	DR	CA
The Netherlands	Administration of AMT-010, an adenoassociated viral vector (AAV) encoding lipoprotein lipase variant S447X (LPLS447X) to LPL deficient patients	humans	lipoprotein lipase variant S447X (LPLS447X)	Adeno-associated virus (AAV)	Academic Medical Center	DR	JRC
The Netherlands	Evaluation of the safety of a Feline Herpes virus, bivalent gene deleted live vaccine, administered as intranasal vaccination to cats	cats	from RNA virus	Feline Herpes Virus Type 1	Pfiser Animal Health	DR	JRC
The Netherlands	A phase 1 dose escalation trial of MDX- 010 in combination with CG1940 and CG8711 in patients with metastatic HRPC	humans	GM-CSF gene	adeno-associated virus 2	VU Medical Center	DR	JRC
The Netherlands	Artificial colonisation of clumping factor B deficient Staphylococcus aureus in the nose	humans	gene encoding ClfB	Staphylococcus aureus	Erasmus MC, University Medical Center Rotterdam	DR	JRC

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
The Netherlands	A double-blind, randomised, placebo controlled dose-escalating phase 1 study to evaluate the safety and immunogenicity of a MVA HIV-1 vaccine administered by three different routes and at three different dosage levels in HIV-uninfected healthy volunteers at lower risk of infection.	humans		Cowpox vaccinia virus	International AIDS Vaccine Initiative, New York, USA	DR	JRC
The Netherlands	Gene therapy in aseptic prosthetic replacement loosening. A phase 1 study	humans		Adenovirus human serotype 5 (Ad5)	Academisch Ziekenhuis Leiden	DR	JRC
The Netherlands	synthesis of a vaccine			Vibrio cholerae	University Hospital Leiden Department of Infectious diseases	DR	JRC
The Netherlands	Adjuvant IL-12 immuno-gene therapy prior to radical prostatectomy in patients with prostate cancer	humans	Interleukin-12 (IL-12)	Adenovirus human serotype 5 (Ad5)	Erasmus MC, University Medical Center Rotterdam	DR	JRC
Norway	Effect of ISIS 3521 antisense in patients with malignant melanoma or patients with NSCLC	humans				CU	Wiley
Norway	A phase III trial of LY9000003 plus Gemcitabine and Cisplatin versus Gemcitabine and Cisplatin in patients with advanced, previously untreated non-small cell lung cancer	humans				CU	Wiley
Norway	Phase I/II trial of vaccine therapy with mRNA-transfected dendritic cells in patients with androgen resistant metastatic prostate cancer	humans				CU	Wiley
Norway	Phase I/II trial of vaccine therapy with mRNA-transfected dendritic cells in patients with metastatic malignant melanoma	humans				CU	Wiley
Poland	Gene Therapy of Human Melanoma. Immunisation of Patients with Autologous Tumor Cells Admixed with Allogeneic Melanoma Cells Secreting Interleukin 6 and Soluble Interleukin 6 Receptor	humans	Interleukin-6 (IL-6) Soluble Interleukin 6 Receptor (sIL-6R)	Retrovirus	Dept. of Cancer Immunology Chair of Oncology Univ. School of Medical Sci. 15 garbary St., Poznan	CU	Wiley
Poland	IGF-I (Insulin like growth factor 1) triple helix cellular therapy of digestive tube tumors	humans	Insulin-Like Growth Factor-1 (IGF-1)	Naked/Plasmid DNA	Jagiellonian University 1st Department of General and GI Surgery 40 Kopernika Str., Karkow	CU	Wiley
Poland	IGF-I (Insulin like growth factor 1) triple helix cellular therapy of brain tumors	humans	Insulin-Like Growth Factor-1 (IGF-1)	Naked/Plasmid DNA	The L. Rydygier Medical University Department of Neurosurgery and Neurotraumatology	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
					9 Sklodowska Str., Bydgoszcz		
Spain	Gene Therapy in Patients with Glioblastoma	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Retrovirus	Universidad Autonoma de Madrid Dept. Biologia Molecular/Centro de Bio Molecular Severo Ochoa Facultad de Ciencias Cantoblanco, Madrid	CU	Wiley
Spain	Gene therapy clinical trial in gastrointestinal cancer	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Adenovirus	Clinica Universitaria de Navarra Division of Gene Therapy Ap. 4209, Pamplona	CU	Wiley
Spain	A phase I clinical trial of AF-IL12 (adenoviral vector coding for interleukin 12 genes) in the treatment of advanced gastrointestinal neoplasms.	humans	Interleukin-12 (IL-12)	Adenovirus	Gene Therapy Unit Clinica Universitaria Ap. 4209, Pamplona	CU	Wiley
Spain	A phase I trial of Intratumoral Injection of Dendritic Cells Engineered to Secrete Interleukin-12 by Recombinant Adenovirus in Patients With Digestive Tumors	humans	Interleukin-12 (IL-12)	Adenovirus	Gene Therapy Unit Clinica Universitaria Ap. 4209, Pamplona	CU	Wiley
Spain	Safety in pregnant does and duration of immunity assessment of a vaccine based on the virus strain 6918VP60.	does		Myxomatosis virus, Leporipoxvirus	Laboratorios Syva, S.A. León	DR	JRC
Spain	Valoration of effects in rapacious birds and european lynx associated with ingestion of rabbits innoculated with a vaccine based on the strain 6918VP60.	birds, lynx, rabbit		Myxomatosis virus, Leporipoxvirus	Laboratorios Syva, S.A. León	DR	JRC
Spain	Field trial of a vaccinie against canine Leishmaniasis		plasmid pORT	orthopoxvirus vaccinia	Consejo Superior de Investigaciones Científicas	DR	JRC
Spain	Development of an Angiogenic Gene Therapy Product for Coronary Artery Disease.	humans		Human adenovirus type 4	Schering Espana SA	DR	JRC
Spain	gene therapy	humans	p53	Human adenovirus type 5	Aventis Pharma (formerly Rhône-Poulenc Rorer S.A.)	DR	CA
Spain	gene therapy	humans	p53	Human adenovirus type 5	Aventis Pharma (formerly Rhône-Poulenc Rorer S.A.)	DR	CA

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Spain	gene therapy	humans	p53	Human adenovirus type 6	Aventis Pharma (formerly Rhône-Poulenc Rorer S.A.)	DR	CA
Spain	synthesis of a vaccine	humans	p53	Human adenovirus type 5	Introgen Therapeutics, Inc	DR	CA
Spain	gene therapy, phase II	humans		Ankara virus	MDS Pharma	DR	CA
Spain	gene therapy	humans		human serotype 5 (Ad5)	Schering Espana SA	DR	CA
Spain	gene therapy, anti-tumor	humans		human serotype 5 (Ad5)	Clínica Universidad de Navarra	DR	CA
Spain	synthesis of a vaccine			Infectious Bovine Rhinotracheitis Virus	Laboratorios Hipra, S.A.	DR	CA
Spain	synthesis of a vaccine			Infectious Bovine Rhinotracheitis Virus	Laboratorios Hipra, S.A.	DR	CA
Spain	synthesis of a vaccine			Infectious Bovine Rhinotracheitis Virus	Laboratorios Hipra, S.A.	DR	CA
Spain	synthesis of a vaccine			Infectious Bovine Rhinotracheitis Virus	Laboratorios Hipra, S.A.	DR	CA
Spain	synthesis of a vaccine			MVA	Transgene S.A.	DR	CA
Spain	synthesis of a vaccine	rabbits		Myxomatosis virus	CISA-INIA, Faculty of Sciences of the University of Oviedo, Faculty of Veterinary of the University of Zaragoza, FEDENCA, Laboratorios Hipra, S.A.	DR	CA
Spain	synthesis of a vaccine	rabbits		Myxomatosis virus	CISA-INIA, Faculty of Sciences of the University of Oviedo, Faculty of Veterinary of the University of Zaragoza, FEDENCA, Laboratorios Hipra, S.A.	DR	CA

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Spain	synthesis of a vaccine	rabbits		Myxomatosis virus	CISA-INIA, Faculty of Sciences of the University of Oviedo, Faculty of Veterinary of the University of Zaragoza, FEDENCA, Laboratorios Hipra, S.A.	DR	CA
Spain	synthesis of a vaccine			Virus gastroenteritis. Porcina	Centro de Biología Molecular CSIC	CU	CA
Spain	introduction of the timidin kinase gene		thymidine kinase gene	Adenovirus	CIFA University of Navarra	CU	CA
Spain	immuno-theray against Hepatitis B			Virus Vaccinia vvWHC and vvWHs	CIFA University of Navarra	CU	CA
Spain	gene therapy			Adenovirus	Lab. Productos Biotecnológicos Fac. Farmacia Univ., Navarra	CU	CA
Spain	gene therapy			HIV	Centro Nacional Biotecnología	CU	CA
Spain	gene therapy			Adenovirus	Clínica Univ. Nav. Dpto. Medicina Interna	CU	CA
Spain	gene therapy		Interleukin-2 (IL-2)	Adenovirus	Area de Terapia Celular Clínica Univ. Navarra	CU	CA
Spain	vector to modify cells			Adenovirus	Dpto. Farmacia y Tecnología Farmaceútica Univ. Navarra	CU	CA
Spain	laboratory tests of a vaccin against myxomatosis			Myxomatosis virus	Laboratorios SYVA	CU	CA
Spain	vaccin against myxomatosis			Myxomatosis virus	University of León	CU	CA
Sweden	Retroviral-Mediated Gene Transfer of CD34-Enriched Bone Marrow and Peripheral Blood Cells During Autologous Stem Cell Transplantation for Multiple Myeloma	humans	Neomycin resistance (NeoR)	Retrovirus	Department of Hematology Huddinge University Hospital, M54 Huddinge	CU	Wiley
Sweden	Intramyocardial injection of phVEGE-A165 as a sole therapy in patients with refractory coronary artery disease	humans	Vascular endothelial growth factor (VEGF)	Naked/Plasmid DNA	Department of Cardiology Karolinska Institute Huddinge University Hospital Novum Stockholm	CU	Wiley

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Sweden	Assessment of the safety and immunogenicity of administering MVA, carrying HIV-1 genes env, gag, and pol in subjects who have previously received plasmid DNA with analogous HIV- 1 genes in HIVIS 01.	humans	HIV-1 genes env, gag, and pol	MVA	Swedish institute for Infectious Disease Control	DR	JRC
Sweden	A Phase I-IIa Study of Dose-escalating Intravesical AdCD40L instillation in Urinary Bladder Carcinoma	humans	human CD40L (CD154) gene	Adenovirus human serotype 5 (Ad5)	Uppsala University, Division of Clinical Immunology, Uppsala	DR	JRC
Switzerland	Gene Therapy for Amyotrophic Lateral Sclerosis (ALS) Using a Polymer Encapsulated Xenogeneic Cell Line Engineered to Secrete hCNTF	humans	Ciliary neurotrophic factor (CNTF)		Lausanne University Medical School CHU Vaudois, Gene Therapy Center Lausanne Dorigny		Wiley
Switzerland	Gene Therapy in Patients with Metastatic Cancer	humans	Interleukin-2 (IL-2)		Kantonsspital, Basel		Wiley
Switzerland	A live recombinant canarypox virus expressing human interleukin-2 (ALVAC/IL-2, vCP277). Phase I/II study in patients with superficial solid tumors	humans	Interleukin-2 (IL-2)	Poxvirus	Multidisciplinary Oncology Centre Centre Hospitalier Universitaire Vaudois Rue du Bugnon 46 Lausanne		Wiley
Switzerland	Gene Therapy in Patients with HIV Infection	humans	HIV-1 Env/Rev	Naked/Plasmid DNA	Zurich		Wiley
Switzerland	Gene Therapy in Patients with Glioblastoma	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Retrovirus	Oncology Clinical Research Novartis Pharma, Basel		Wiley
Switzerland	Gene Therapy in Patients with Cystic Fibrosis	humans	Cystic fibrosis transmembrane conductance regulator (CFTR)	Adenovirus	Hôpital Cantonal Division de PNeumologie Geneve		Wiley
Switzerland	Gene Therapy of Severe Combined Immune Deficiency Due to Adenosine Aeaminase (ADA) Deficiency	humans	Adenosine deaminase (ADA)	Retrovirus	University Children's Hospital Immunology/Haematology Zurich		Wiley
Switzerland	Gene Therapy in Patients with Glioblastoma	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Retrovirus	Univ. Canton Hospital Clinic for Neurosurgery, Bern		Wiley
Switzerland	adenovirus-p53 gene therapy in non-small cell lung cancer patients	humans	p53	Adenovirus	Division of Oncology University Hospital Basel University, Basel		Wiley
Switzerland	Gene therapy in patients with amyotrophic lateral sclerosis	humans	Ciliary neurotrophic factor (CNTF)		Lausanne		Wiley
Switzerland	Gene therapy in patients with superficial solid tumours	humans	Granulocyte-macrophage colony stimulating factor	Poxvirus			Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
			(GM-CSF)				
Switzerland	Gene therapy in patients with recurrent squamous cell carcinoma of the head and neck (SCCHN)	humans	p53	Adenovirus	Lausanne		Wiley
Switzerland	adenovirus-p53 gene therapy in non-small cell lung cancer patients	humans	p53	Adenovirus	Division of Oncology University Hospital Basel University Basel		Wiley
Switzerland	Gene therapy in patients with malignant melanoma	humans	Interleukin-2 (IL-2)				Wiley
Switzerland	Gene therapy in patients with recurrent squamous cell carcinoma of the head and neck (SCCHN)	humans	p53	Adenovirus			Wiley
Switzerland	Gene therapy in patients with advanced cancers	humans	MAGE-1 MAGE-3	Poxvirus			Wiley
Switzerland	Gene therapy in patients with metastasis from solid tumours	humans	Interferon-gamma (IFN-g)	Adenovirus	Lausanne		Wiley
Switzerland	Gene therapy in patients with colorectal cancer metastatic to the liver	humans	p53	Adenovirus			Wiley
Switzerland	Gene therapy in patients with advanced pancreatic carcinoma	humans	Cytochrome p450		Bern		Wiley
Switzerland	Gene therapy in patients with melanoma	humans	Melanoma differentiation associated protein 7 (MDA-7)	Vaccinia virus	Basel		Wiley
Switzerland	Gene therapy in patients with advanced cancers	humans	MUC-1 Interleukin-2 (IL-2)	Vaccinia virus	Basel		Wiley
Switzerland	Gene therapy in patients with malignant melanoma	humans	Interleukin-12 (IL-12)	Naked/Plasmid DNA	Zurich		Wiley
Switzerland	Gene therapy in patients with HIV infection	humans	HIV genes	Poxvirus			Wiley
Switzerland	Gene therapy in patients with chronic renal insufficiency	humans	Erythropoietin (EPO)		Lausanne		Wiley
Switzerland	Gene therapy in patients with malignant melanoma	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF) B7.2	Adeno-associated virus	Zurich		Wiley
Switzerland	Gene therapy in patients with metastatic melanoma and advanced solid tumour cancers	humans	Interleukin-2 (IL-2)	Adenovirus			Wiley
Switzerland	Gene therapy in patients with severe peripheral artery occlusive disease (PAOD)	humans	Fibroblast growth factor (FGF)	Naked/Plasmid DNA	Bern		Wiley
Switzerland	Gene therapy in patients with severe peripheral artery	humans	Fibroblast growth factor	Naked/Plasmid			Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
	occlusive disease (PAOD)		(FGF)	DNA			
Switzerland	Phase I/II clinical trial of biologic therapy with intratumoral TG1042 (adenovirus-interferon-gamma) in patients with advanced cutaneous T-cell lymphomas (CTCL) - mycosis fungoides and other CTCL - an multilesional cutaneous B-cell lymphomas (CBCL)	humans	Interferon-gamma (IFN-g)	Adenovirus	Department of Dermatology, University Hospital Zurich, Gloriastrasse 31 Zurich		Wiley
Switzerland	Gene therapy in patients with breast cancer	humans	MUC-1 Interleukin-2 (IL-2)	Vaccinia virus			Wiley
Switzerland	Gene therapy in patients with non-small cell lung cancer	humans	MUC-1 Interleukin-2 (IL-2)	Vaccinia virus	Basel		Wiley
Switzerland	Gene therapy in patients with malignant melanoma	humans	Melanoma antigen Melan-A	Naked/Plasmid DNA	Zurich		Wiley
Switzerland	Gene therapy in patients with HIV infection	humans	HIV clade C	Vaccinia virus	Lausanne		Wiley
Switzerland	Gene therapy in patients with HIV infection	humans	HIV clade A HIV-1 Gag	Vaccinia virus	Lausanne		Wiley
Switzerland	Immunotherapy for Stage I cervical carcinoma	humans	Interleukin-2 (IL-2)	Vaccinia virus	Geneva		Wiley
Switzerland	Immunotherapy for advanced cervical carcinoma	humans	Interleukin-2 (IL-2)	Vaccinia virus	Geneva		Wiley
Switzerland	Gene therapy for critical limb ischaemia	humans	Vascular endothelial growth factor (VEGF)	Naked/Plasmid DNA	Bern		Wiley
Switzerland	Gene therapy for intermittent claudication	humans	NV1FGF	Naked/Plasmid DNA	Bern		Wiley
Switzerland	Anti HIV vaccine	humans	HIV clade C	Vaccinia virus	Lausanne		Wiley
Switzerland	Gene therapy for Huntingdon's disease	humans	Ciliary neurotrophic factor (CNTF)	Naked/Plasmid DNA	Ecole polytechnique Federale de Lausanne		Wiley
Switzerland	TG 4010.04 Randomised, multicenter, phase II study evaluating two doses of TG 4010 (MVA-MUC-1-IL-2) in patents with metastatic breast cancer	humans	MVA-MUC-1-IL-2		Transgene SA, 11, rue de Molsheim F-67082 Strasbourg		CA
Switzerland	TG 4010.05 Randomised, multicenter, phase II study evaluating the clinical efficacy of TG 4010 (MVA-MUC-1-IL-2) in association with chemotherapy in patients with non small cell lung cancer	humans	MVA-MUC-1-IL-3		Transgene SA, 11, rue de Molsheim F-67082 Strasbourg		CA

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
Switzerland	TG4001.06 Phase II study of TG4001 (MVA-HPV-IL2) in women with HPV16 Grade 3 vulvar intraepithelial neoplasia (VIN3) except genital bowen's disease	humans	MVA-HPV-IL2		Transgene SA, 11, rue de Molsheim F-67082 Strasbourg		CA
Switzerland	Phase I trial to assess the safety of 4 ml DNA C (IM), and the safety and immunogenicity of DNA C followed by NYVAC C (IM) in an open, randomised comparison to NYVAC C alone in healthy volunteers at low risk of HIV infection	humans			CHUV Lausanne		CA
Switzerland	Etude clinique ouverte de phase I visant à évaluier la sûreté du NYVAC-B-vaccin thérapeutique contrle le VIH-1-chez des patients traités avec succès par HAART'der EuroVacc foundation	humans			CHUV Lausanne		CA
United Kingdom	Use of a recombinant vaccinia virus for therapy of cervical cancer	humans	Human papilloma virus (HPV)	Vaccinia virus	Department of Medicine University of Wales College of Medicine, Heath Park Cardiff	CU	Wiley
United Kingdom	Transfer of the Human Multi-drug Resistance Gene into the Haemopoietic Cells of Patients Undergoing High Dose Therapy and Autologous Stem Cell Transplantation for Malignant Lymphoma	humans	Multi-Drug Resistance-1 (MDR-1)	Retrovirus	University College London Medical School Department of Haematoloogy Chenies Mews, 98; LONDON	CU	Wiley
United Kingdom	Gene Therapy for Cystic Fibrosis. Assessment of the Safety and Efficacy of Liposome-Mediated DNA Transfer to the Nasal Epithelium	humans	Cystic fibrosis transmembrane conductance regulator (CFTR)	Lipofection	Royal Brompton Nat. Heart & Lung Hospital London	CU	Wiley
United Kingdom	The treatment of metastatic malignant melanoma with autologous melanoma cells that have been genetically engineered to secret IL-2	humans	Interleukin-2 (IL-2)	Retrovirus	Institute of Cancer Research Royal Marsden NHS Trust Downs Road Sutton, Surrey	CU	Wiley
United Kingdom	Gene Therapy for metastatic melanoma: Assessment of expression of DNA constructs directly injected into metastases	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Retrovirus	Institute of Molecular Medicine John Radcliffe Hospital Imperial Cancer Research Fund Headington, Oxford	CU	Wiley
United Kingdom	Gene Therapy for melanoma	humans	LacZ	Naked/Plasmid DNA	Institute of Molecular Medicine John Radcliffe Hospital Imperial Cancer Research Fund	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
					Headington, Oxford		
United Kingdom	A pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach	humans	Specific anti-Idiotype	Naked/Plasmid DNA	MRC Cambridge Center for protein engineering Cambridge	CU	Wiley
United Kingdom	Towards gene therapy for cystic fibrosis	humans	Cystic fibrosis transmembrane conductance regulator (CFTR)	Lipofection	MRC Clinical Sciences Centre Hammersmith Hospital Du Cane Road London	CU	Wiley
United Kingdom	Towards gene therapy for cystic fibrosis	humans	Cystic fibrosis transmembrane conductance regulator (CFTR)	Lipofection	MRC Clinical Sciences Centre Hammersmith Hospital Du Cane Road, London	CU	Wiley
United Kingdom	Use of gene transfer to determine the role of tumour cells in bone marrow used for autologous transplantation and the efficiency of immunomagnetic "purging" the bone marrow	humans	LNL-6/neo G1N-neo	Retrovirus	Imperial Cancer Research Fund Bristol Bristol	CU	Wiley
United Kingdom	Gene Therapy of Mucopolysaccharidosis Type I (Hurlers syndrome)	humans	Alpha-1-iduronidase (IDUA)	Retrovirus	Paterson Institute for Cancer Research Christie Hospital NHS Trust Department of Experimental Haematology, Manchester	CU	Wiley
United Kingdom	Adenosine deaminase gene transfer in a child with severe combined immunodeficiency syndrome	humans	Adenosine deaminase (ADA)	Retrovirus	Institute of Child Health Dept. of Immunology 30 Guilford Street London	CU	Wiley
United Kingdom	Gene Therapy in Patients with Colon Adenocarcinoma	humans			Wellcome Research Laboratories Dept of Molecular Sciences Beckenham	CU	Wiley
United Kingdom	Gene therapy for Cystic Fibrosis Delivery to nasal epithelium and lung by nebulisation of the pCFICFTR/#67	humans	Cystic fibrosis transmembrane conductance regulator (CFTR)	Lipofection	Department of Gene Therapy Imperial College at National Heart and Lung Institute London	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
United Kingdom	Gene Therapy Research for Cystic Fibrosis	humans	Cystic fibrosis transmembrane conductance regulator (CFTR)	Lipofection	University of Edinburgh Molecular Medicine Center Western General Hospital Crewe Road, Edinburgh	CU	Wiley
United Kingdom	Genetic prodrug activation therapy for breast cancer	humans	Cytosine deaminase	Naked/Plasmid DNA	Hammersmith Hospital Imperial Cancer Research Fund Dept. of Cancer Medicine, Oncology Group, Du Cane Road, London	CU	Wiley
United Kingdom	A study of dose requirements, safety and local efficacy of intratumoral injection of the genetically modified non-virulent herpes simplex virus HSV ICP 34.5 negative mutant 1716 into accessible soft tissue nodules of secondary malignant melanoma	humans	ICP34.5 deleted	Herpes simplex virus	Department of Dermatology Robertson Building University of Glasgow Glasgow	CU	Wiley
United Kingdom	The use of MetXia-P450 for the treatment of advanced breast cancer (Phase I/II intratumoral)	humans	Cytochrome p450	Retrovirus	ICRF Medical Oncology Unit Churchill Hospital Headington, Oxford	CU	Wiley
United Kingdom	A phase I/II study of hepatic artery infusion with wt p53-CMV-Ad in primary metastatic liver tumours	humans	p53	Adenovirus	Hammersmith Hospital Liver Surgery Section Du Cane Rd, London	CU	Wiley
United Kingdom	A Phase I/II pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach (i.m.)	humans	lymphoma idiotype Fragment C of tetanus toxin	Naked/Plasmid DNA	Cancer research UK Oncology Unit Cancer Sciences building Mall Point 824 Southampton General Hospital Tremona Road, Southampton	CU	Wiley
United Kingdom	Use of a retrovirus carrying human cytochrome p450 for the treatment of ovarian cancer (Phase I intra-abdominal)	humans	Cytochrome p450	Retrovirus	Northern General Hospital Sheffield	CU	Wiley
United Kingdom	Gene directed enzyme prodrug therapy for the treatment of head and neck cancer (Phase I intratumoral)	humans	Nitroreductase	Adenovirus	CRC Institute for Cancer Studies University of Birmingham Birmingham	CU	Wiley
United Kingdom	Gene directed enzyme prodrug therapy for the treatment of liver cancer (Phase I intratumoral)	humans	Nitroreductase	Adenovirus	CRC Institute for Cancer Studies University of Birmingham Birmingham	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
United Kingdom	Phase I trial of immunotherapy with adenovirus-interferon-gamma in malignant melanoma (intratumoral)	humans	Interferon-gamma (IFN-g)	Adenovirus	St. George's Hospital London	CU	Wiley
United Kingdom	A phase II/III trial of chemotherapy alone versus chemotherapy plus Adp53 in ovarian cancer (intraperitoneal)	humans	p53	Adenovirus	Royal Marsden Hospital London	CU	Wiley
United Kingdom	The safety and effects of Ad5.1 mediated human FGF-4 gene transfer in patients with peripheral arterial occlusive disease (PAOD) Fontaine stage III (Phase I i.m.)	humans	Fibroblast growth factor (FGF)	Adenovirus	St. George's Hospital London	CU	Wiley
United Kingdom	A multiple ascending dose study evaluating the safety and gene transduction into malignant cells after administration of E1A-lipid complex by intratumoral injection with unresectable or metastatic head and neck tumours	humans	E1A	Lipofection	The John Radcliffe Hospital, Oxford Guy's and St Thomas's Cancer Centre London	CU	Wiley
United Kingdom	Phase I, Open-Label, Dose-Escalation Trial of Intra-Tumoral Injection with an E1B Attenuated Adenovirus ONYX-015, into Recurrent and Locally Advanced p53(-) Squamous Cell Tumours of the Head and Neck	humans	E1B deleted	Adenovirus	Beatson Oncology Centre Glasgow	CU	Wiley
United Kingdom	Phase II trial of pre-operative intratumoral injection with an E1B attenuated adenovirus in patients with resectable head and neck tumours	humans	E1B deleted	Adenovirus	Beatson Oncology Centre Glasgow	CU	Wiley
United Kingdom	A phase II trial of intravenous cisplatin, 5-FU and intratumoral injection with ONYX-015 into recurrent, chemotherapy naive squamous cell tumours of the head and neck	humans	E1B deleted	Adenovirus	Beatson Oncology Centre Glasgow	CU	Wiley
United Kingdom	Phase I, Open-Label, Dose-Escalation Trial of Intraperitoneal Injection with an E1B Attenuated Adenovirus in patients with recurrent/refractory ovarian carcinomas	humans	E1B deleted	Adenovirus	Beatson Oncology Centre Glasgow	CU	Wiley
United Kingdom	Phase I study in patients with recurrent metastatic squamous cell carcinoma of the head and neck using SCH 58500 (rAd/p53)	humans	p53	Adenovirus	Institute of Cancer Research Royal Marsden Hospital	CU	Wiley
United Kingdom	A Phase I dose-escalation study of intratumoral injection with modified HSV Type I (ICP 34.5-) into primary and recurrent malignant glioma	humans	ICP34.5 deleted	Herpes simplex virus	Beatson Oncology Centre Western Infirmary Glascow	CU	Wiley
United Kingdom	A Phase I dose-escalation study of intratumoral injection with modified HSV Type I (ICP 34.5-) into	humans	ICP34.5 deleted	Herpes simplex virus	Beatson Oncology Centre Western Infirmary	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
	primary and recurrent malignant glioma				Glascow		
United Kingdom	GTI 0115 radiation and infection of murine cells producing HSV TK vector followed by intravenous ganciclovir against the efficacy of surgery and radiation in the treatment of newly diagnosed previously untreated glioblastoma (tumour site)	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Retrovirus	Beatson Oncology Centre Glasgow	CU	Wiley
United Kingdom	A clinical trial with Ad-5CMV-p53 vector in patients with ascites formation	humans	p53	Adenovirus	Royal Marsden Hospital London	CU	Wiley
United Kingdom	Phase II study of immunotherapy of advanced breast cancer by repeated intramuscular injection of recombinant vaccinia viruses containing sequences coding for human MUC-1 and IL2 (TG1031)	humans	MUC-1 Interleukin-2 (IL-2)	Vaccinia virus	Guy's Hospital London	CU	Wiley
United Kingdom	A multiple ascending dose study evaluating the safety and the gene transduction into malignant cells after the administration of EIA-lipd complex by intra-peritoneal administration in patients with epithelial ovarian cancer who over express HER-2/neu	humans	E1A HER-2/neu	Lipofection	The John Radcliffe Hospital, Oxford Guy's and St Thomas's Cancer Centre London	CU	Wiley
United Kingdom	A pilot study of recombinant CEA vaccinia virus vaccine with post vaccination CEA peptide challenge in combination with 5-fluorouracil and folinic acid in the treatment of colorectal cancer (Phase I subcutaneous)	humans	Carcinoembryonic antigen (CEA)	Vaccinia virus	Queen Elizabeth Hospital Birmingham	CU	Wiley
United Kingdom	A phase I study of intraperitoneal administration of a replication deficient adenovirus carrying a nitroreductase gene in ovarian cancer patients	humans	Nitroreductase	Adenovirus	University Hospital NHS Trust Birmingham	CU	Wiley
United Kingdom	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Cervical intraepithelial neoplasia III	humans	Human papilloma virus (HPV) E6 and E7	Poxvirus	University of Cardiff Cardiff	CU	Wiley
United Kingdom	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Cervical intraepithelial neoplasia III	humans	Human papilloma virus (HPV) E6 and E7	Poxvirus	University of Cardiff Cardiff	CU	Wiley
United Kingdom	A proposal to study the efficacy of transplantation of autologous retroviral transduced bone marrow in patients homozygous for the W402X mutation (Hurlers syndrome)	humans	pLX	Retrovirus	Royal Manchester Children's Hospital Manchester	CU	Wiley
United Kingdom	Gene therapy for metatstatic melanoma: assessment of expression of DNA constructs directly injected into metastases.	humans	Interleukin-2 (IL-2)	Naked/Plasmid DNA	ICRF Medical Oncology Unit Churchill Hospital Headington, Oxford	CU	Wiley
United Kingdom	A phase II trial of intravenous cisplatin, 5-FU and intratumoral injection with ONXY-105 into recurrent,	humans	E1B deleted	Adenovirus	Beatson Oncology Centre Glasgow	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
	naive squamous cell tumours of the head and neck						
United Kingdom	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Cervical intraepithelial neoplasia III	humans	Human papilloma virus (HPV) E6 and E7	Vaccinia virus	Department of Medicine University of Wales College of Medicine, Heath Park, Cardiff	CU	Wiley
United Kingdom	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Cervical intraepithelial neoplasia III			Vaccinia virus		CU	Wiley
United Kingdom	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat vulval intraepithelial neoplasia III	humans	Human papilloma virus (HPV) E6 and E7	Vaccinia virus	Department of Medicine University of Wales College of Medicine, Heath Park, Cardiff	CU	Wiley
United Kingdom	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat ano-genital intraepithelial neoplasia III	humans	Human papilloma virus (HPV) E6 and E7	Vaccinia virus	Department of Medicine University of Wales College of Medicine, Heath Park, Cardiff	CU	Wiley
United Kingdom	A study of the safety of the modified Herpes Simplex virus (HSV 1716) when injected into tumour bearing brain following resection of recurrent or newly diagnosed high grade glioma	humans	ICP34.5 deleted	Herpes simplex virus	Beatson Oncology Centre Western Infirmary Glasgow	CU	Wiley
United Kingdom	A pilot study of donor idiotypic vaccination for the purpose of targeted post-transplant immunotherapy following allogenic bone marrow transplantation for multiple myeloma	humans	myeloma idiotype Fragment C of tetanus toxin	Naked/Plasmid DNA	Cancer research UK Oncology Unit Cancer Sciences building Mall Point 824 Southampton General Hospital Tremona Road, Southampton	CU	Wiley
United Kingdom	Phase I/II study of idiotypic vaccination for multiple myeloma using a genetic approach (MMIFTT)	humans	myeloma idiotype Fragment C of tetanus toxin	Naked/Plasmid DNA	Cancer research UK Oncology Unit Cancer Sciences building Mall Point 824 Southampton General Hospital Tremona Road, Southampton	CU	Wiley
United Kingdom	Phase I/II study of idiotypic vaccination for chronic lymphocytic leukaemia using a genetic approach (CLLIFT)	humans	leukaemia idiotype	Naked/Plasmid DNA	Cancer research UK Oncology Unit Cancer Sciences building Mall Point 824 Southampton General Hospital	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
					Tremona Road, Southampton		
United Kingdom	A Phase III study of quadruple HAART followed by double-blind randomisation to HIV vaccination with ALVAC-HIV and Remune or placebo	humans	HIV-1 Env	Poxvirus	Department of HIV & Opportunistic Infections GlaxoSmithKline Research and Development GlaxoSmithKline, Greenford Road Greenford	CU	Wiley
United Kingdom	A phase I, open label, dose escalation trial to assess the safety and immunogenicity of DISC-GMCSF in patients with metastatic melanoma	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Herpes simplex virus	ICRF Medical Oncology Unit Churchill Hospital Headington, Oxford	CU	Wiley
United Kingdom	Gene therapy protocol for the evaluation of the safety, biodistribution and efficacy of trovax in patients with metastatic colorectal cancer (Phase I i.m)	humans	Oncofoetal antigen 5T4	Vaccinia virus	Christie Hospital NHS Trust Wilmslow Road, Manchester	CU	Wiley
United Kingdom	A phase I dose escalation trial of an E1B attenuated adenovirus as an intravesical therapy for recurrent superficial/muscle invasive bladder cancer	humans	E1B deleted	Adenovirus	ICRF Cancer Medicine Research Unit, St James University Hospital Beckett Street, Leeds	CU	Wiley
United Kingdom	Randomised multi-centre trial evaluating two different vaccination schedules of MVA-MUC-1-IL-2 in women with metastatic breast cancer (phase II i.m)	humans	MUC-1 Interleukin-2 (IL-2)	Vaccinia virus	Guy's Hospital London	CU	Wiley
United Kingdom	Phase I study of melanoma polyepitope DNA and melanoma poly-epitope modified vaccinia Ankara in patients with melanoma	humans	Mel3	Vaccinia virus	ICRF Medical Oncology Unit Churchill Hospital Headington, Oxford	CU	Wiley
United Kingdom	Treatment of leukaemic relapse after allogenic stem cell transplantation by HSV-tk transduced donor lymphocyte tranfusions	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Retrovirus		CU	Wiley
United Kingdom	Phase I clinical gene therapy protocol for X-linked Severe Combined Immuno deficiency (X-SCID)	humans	Gamma c common chain receptor	Retrovirus	Institute of Child Health 30 Guildford Street, London	CU	Wiley
United Kingdom	Phase I gene therapy protocol for X-linked Chronic granulomatous disease	humans	gp91phox	Retrovirus	Institute of Child Health 30 Guildford Street, London	CU	Wiley
United Kingdom	A phase I, randomised, double-blind, placebo controlled, escalating dose, multicentre study of Ad2/Hypoxia Inducible factor gene transfer administered by intramyocardial injection during coronary artery bypass grafting surgery in patients	humans	Hypoxia inducible factor (HIF)-1ahpha	Adenovirus	Department of Cadiovascular Medicine John Radcliffe Hospital Headington Oxford	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
	with incomplete revascularisation						
United Kingdom	A randomised phase I trial of intravenous CI-1042 with or without entanercept in patients with metastatic carcinoma	humans	p53	Adenovirus		CU	Wiley
United Kingdom	A phase I/II study of immunotherapy for patients with metatstatic melanoma using dendritic cells transfected with a plasmid encoding two melanoma antigens	humans	Melanoma antigen MART-1 Melanoma antigen gp100	Naked/Plasmid DNA		CU	Wiley
United Kingdom	A Phase II trial of preoperative intratumoural injection with HSV1716 in patients with resectable squamous cell tumours of the head and neck	humans	ICP34.5 deleted	Herpes simplex virus	University of Glasgow Dept. of Neurovirology Insititute of Neurological Sciences Southern General Hospital NHS Trust GLASGOW	CU	Wiley
United Kingdom	A phase I study to evaluate the safety, tolerability and immunogenicity of two administratons of either plasmid DNA (pSG.HBs) versus placebo or modified vaccinia virus Ankara (MVA.HBs) versus placebo followed by two boost administrations of MVA.HBs expressing hepatitis B surface antigen in healthy male volunteers	humans	HBsAg	Vaccinia virus		CU	Wiley
United Kingdom	A pilot study of the safety and immunogenicity of a candidate HIV-1 clade A DNA vaccine, pTHr.HIVA, given by needle injection into the deltoid muscle in HIV-1 seropositive subjects receiving highly active antiretroviral therapy	humans	HIV-1 Gag Antisense Pol 1 HIV-1 Env	Naked/Plasmid DNA		CU	Wiley
United Kingdom	A phase II randomised double-blind, placebo-controlled, parallel group, efficay and safety Study of NV1FGF in patients with severe peripheral artery occlusive disease	humans	Fibroblast growth factor (FGF)	Naked/Plasmid DNA		CU	Wiley
United Kingdom	Gene directed enzyme prodrug therapy for the treatment of prostate cancer (Phase I intratumoural)	humans	Nitroreductase	Adenovirus	CRC Institute for Cancer studies, University of Birmingham, Birmingham	CU	Wiley

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United Kingdom	A phase II, multicentre, double-blind, placebo controlled, dose finding study of ZYC101a in the treatment of high-grade squamous intra-epithelial lesions of the uterine cervix	humans	Human papilloma virus (HPV) E6 and E7	Naked/Plasmid DNA	Gynaecological Oncology Centre Hammersmith Hospital NHS Trust DuCane Rd, London	CU	Wiley
United Kingdom	A phase I, multidose Study to evaluate the safety of Intramuscular injections of HER-2 DNA in patients with metastatic breast cancer	humans	HER-2	Naked/Plasmid DNA		CU	Wiley
United Kingdom	The use of cDNA vaccine encoding the human MUC-1 gene in the treatment of patients with advanced breast cancer- a phase I/II study	humans	MUC-1	Naked/Plasmid DNA		CU	Wiley
United Kingdom	TA-HPV recombinant vaccinia virus expressing the human papillomavirus 16 and 18 E6 and E7 proteins: application to amend currently approved protocol to add a clinical trial involving prime-boost strategy of TA-CIN administered in association with TA-HPV in high grade ano-genital intraepithelial neoplasia (AGIN) patients (PB-HPV/01)	humans	Human papilloma virus (HPV) E6 and E7	Vaccinia virus		CU	Wiley
United Kingdom	Study of transfection efficacy and safety of MetXia-OB83 in patients with cutaneous lesions of breast cancer or melanoma	humans	Cytochrome p450	Retrovirus	CRUK Clinical Trials Unit Institute of Cancer Studies Vincent Drive Edgbaston, Birmingham	CU	Wiley
United Kingdom	An upward titration study of transfection efficacy and safety of Metxia OB83 in patients with adenocarcinoma of the prostate	humans	Cytochrome p450	Retrovirus		CU	Wiley
United Kingdom	First administration to man of an oncolytic herpesvirus vector containing a transgene for granulocyte macrophage colony stimulating factor (Oncovex GM-CSF)- A study of its safety, biodistribution and biological activity	humans	ICP34.5 deleted ICP47 deleted Granulocyte-macrophage colony stimulating factor (GM-CSF)	Herpes simplex virus	Imperial College School of Medicine Hammersmith Hospital Campus DuCane Road London	CU	Wiley
United Kingdom	VTP-1/01: A phase I/II trial of intravenous vs. hepatic arterial infusion of an E1A-CR2 deleted adenovirus (VTP-1) in patients with inoperable metastatic colorectal carcinoma	humans		Adenovirus		CU	Wiley
United Kingdom	A phase I trial of replication-competent herpes simlex virus (ICP 34.5 null mutant 1716) in patients with inoperable malignant pleural mesothelioma	humans		Herpes simplex virus	Department of Medical Oncology University of Glasgow Garscube Estate Switchback Road, Glasgow	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
United Kingdom	A phase I trial of PolyMEL, a polyepitope DNA vaccine in the treatment of metastatic melanoma patients	humans		Naked/Plasmid DNA	Division of cancer medicine research CRUK Clinical centre St James University hospital Beckett Street, Leeds	CU	Wiley
United Kingdom	A recombinant vaccinia Ankara (MVA)-based vaccine encoding Epstein Barr virus target antigens: Phase I dose escalation trial to determine immunogenicity and toxicity in patients with EBV+ malignancy	humans		Vaccinia virus	CRUK Clinical trials unit Institute of cancer studies Vincent drive Edgbaston, Birmingham	CU	Wiley
United Kingdom	Percutaneous Intramyocardial Gene therapy against myocardial ischaemia with phVEGF-A165SR- A double blind placebo controlled study	humans	Vascular endothelial growth factor (VEGF)	Naked/Plasmid DNA		CU	Wiley
United Kingdom	A phase I trial of polyHER2neu- a polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of breast cancer	humans	HER-2	Naked/Plasmid DNA	Division of cancer medicine research CRUK Clinical centre St James University hospital Beckett Street, Leeds	CU	Wiley
United Kingdom	A phase I/II study of DNA vaccination against a CMV/FrC of tetanus toxin fusion gene in allograft donors and recipients	humans	CMV pp65	Naked/Plasmid DNA	Cancer Research UK Oncology Unit Cancer Sciences Building Mail Point 824 Southampton General Hospital Tremona Road, Southampton	CU	Wiley
United Kingdom	A phase I/II prospective study of immunogene therapy with a liposomally encapsulated replication incompetent Semliki Forest virus (SFV) vector carrying the human interleukin-12 gene and administered intratumourally in patients with recurrent or progressing glioblastoma multiforme	humans	Interleukin-12 (IL-12)	Semliki forest virus		CU	Wiley
United Kingdom	Phase I/II study to determine the optimum dose and dosing regimen then to assess the efficacy of a poly-epitope pharmaccine (therapeutic vaccine) involving pSG2, Mel 3 and MVA.Mel3, in patients with stage II or Stage IV metastatic melanoma	humans	pSG2 Mel3	Naked/Plasmid DNA	ICRF Medical Oncology Unit Churchill Hospital Headington Oxford	CU	Wiley
United Kingdom	Phase I clinical gene therapy protocol for adenosine deaminase deficiency	humans	Adenosine deaminase (ADA)	Retrovirus	Institute of Child Health 30 Guildford Street, London	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
United Kingdom	Clinical trial of E1B-deleted adenovirus (dll520) gene therapy for hepatocellular carcinoma	humans	E1B deleted	Adenovirus	Division of Surgery Anaesthetics and Intensive Care Imperial College School of Medicine Hammersmith Hospital Campus, London	CU	Wiley
United Kingdom	Phase II study of Trovax in colorectal cancer patients undergoing surgery for resectable liver metastases	humans	Oncofoetal antigen 5T4	Poxvirus		CU	Wiley
United Kingdom	Gene therapy for bowel cancer that has spread for the skin	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Herpes simplex virus	Imperial College School of Medicine Hammersmith Hospital Campus DuCane Road, London	CU	Wiley
United Kingdom	Gene therapy for breast cancer that has spread for the skin	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Herpes simplex virus	Imperial College School of Medicine Hammersmith Hospital Campus DuCane Road, London	CU	Wiley
United Kingdom	Gene therapy for squamous cell head and neck cancer that has spread to the skin	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Herpes simplex virus	Imperial College School of Medicine Hammersmith Hospital Campus DuCane Road, London	CU	Wiley
United Kingdom	Gene therapy for malignant melanoma	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Herpes simplex virus	Imperial College School of Medicine Hammersmith Hospital Campus DuCane Road, London	CU	Wiley
United Kingdom	Gene therapy for oesophageal cancer that has spread to the skin	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Herpes simplex virus	Imperial College School of Medicine Hammersmith Hospital Campus DuCane Road, London	CU	Wiley
United Kingdom	Gene therapy for pancreatic cancer that has spread to the skin	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Herpes simplex virus	Imperial College School of Medicine Hammersmith Hospital Campus DuCane Road, London	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
United Kingdom	Gene therapy for stomach cancer that has pread to the skin	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Herpes simplex virus	Imperial College School of Medicine Hammersmith Hospital Campus DuCane Road, London	CU	Wiley
United Kingdom	A randomised phase II trial of replication-competent herpes simplex virus (ICP 34.5 null mutant) HSV1716 in recurrent glioblastoma	humans	ICP34.5 deleted	Herpes simplex virus	Beatson Oncology centre Glasgow	CU	Wiley
United Kingdom	A phase I study of NYVAC C in healthy volunteers at low risk of HIV infection (EV01)	humans	HIV clade C	Vaccinia virus	Imperial College London	CU	Wiley
United Kingdom	A phase I/II study of DNA vaccination with a CEA/pDOM fusion gene in patients with carcinoma expressing CEA	humans	CAP-1 peptide from CEA	Naked/Plasmid DNA	Cancer Research UK Oncology Unit Cancer Sciences Building Mail Point 824 Southampton General Hospital Tremona Road, Southampton	CU	Wiley
United Kingdom	Gene therapy protocol for the evaluation of the safety and efficacy of TroVax in conjunction with chemotherapy in patients with metastatic colorectal cancer	humans	Oncofoetal antigen 5T4	Vaccinia virus	Christie Hospital Manchester	CU	Wiley
United Kingdom	A phase I clinical gene therapy trial for X-SCID using umbilical cord blood	humans	Common gamma chain	Retrovirus	Institute of child health London	CU	Wiley
United Kingdom	a pilot study to evaluate the safety, tolerability and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA delivered to HIV-1 sero-positive adults receiving HAART	humans	HIV clade A HIV-1 Gag-Pol-Nef-Env	Vaccinia virus	MRC Human immunology Unit, John Radcliffe Hospital Oxford	CU	Wiley
United Kingdom	Phase I/II study-first administration of dendritic cells transduced with ImmunoVEXTRI-Melan to patients with metastatic or inoperable melanoma	humans	hTyrosinase hMART1 hGP100	Herpes simplex virus	St George's Hospital Medical School London	CU	Wiley
United Kingdom	An open label study of TroVax given in conjunction with 5-flurorouracil/Leukovorin/Oxaliplatin: safety and immunogenicity before, during and after chemotherapy (TV2)	humans	Oncofoetal antigen 5T4	Vaccinia virus	University of Leeds school of Medicine Leeds	CU	Wiley
United Kingdom	A phase II trial to evaluate efficacy and safety of intramuscular injections of HER-2 DNA Autovac in patients with metastatic or locally advanced breast cancer	humans	HER-2	Naked/Plasmid DNA	Hammersmith hospital London	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
United Kingdom	A phase I/II safety study of MetXia-OB83 in patients with pancreatic cancer	humans	Cytochrome p450	Retrovirus	Royal Liverpool University Hospital Liverpool	CU	Wiley
United Kingdom	A phase I study of immunotherapy for patients with metastatic melanoma using dendritic cells transfected with a plasmid encoding two melanoma antigens	humans	Melanoma antigen MART-1 gp-100	Naked/Plasmid DNA	CRUK Birmingham	CU	Wiley
United Kingdom	A phase I trial to assess the safety of DNA C, and the safety and immunogenicity of DNA C followed by NYVAC C in an open, randomised comparison to NYVAC C alone in healthy colunteers at low risk of HIV infection (EV02)	humans	HIV clade C HIV-1 Gag-Pol-Nef-Env	Naked/Plasmid DNA	Imperial College London	CU	Wiley
United Kingdom	First administration of dendritic cells transduced with ImmunoVEXTri-Melan to patients with metastatic or inoperable melanoma, preliminary assessment of safety, biodistribution and indicators of efficacy	humans	hTyrosinase hMART1 hGP100	Herpes simplex virus	St George's hospital Medical School London	CU	Wiley
United Kingdom	A phase II study immunologically evaluating 5T4-MVA (TroVax) in patients undergoing surgical resection of colorectal liver metastases	humans	Oncofoetal antigen 5T4	Vaccinia virus	Christie research centre Manchester	CU	Wiley
United Kingdom	A cancer research UK phase I trial of AEG35156/GEM640 (XIAP antisense) administered as a 7 day continuous intravenous infusion in patients with advanced tumours	humans	Antisense DNA to human X-linked inhibitor of apoptosis		Christie hospital Manchester	CU	Wiley
United Kingdom	A phase I/II trial of DNA vaccine with a PSMA27/pDom fusion gene given by intramuscular injection in HLA A2+ patients with prostate carcinomas with or without elctroporation	humans	Prostate specific membrane antigen (PSMA)/pdom fusion gene	Naked/Plasmid DNA	Cancer Research UK Oncology Unit, Cancer Sciences Building, Southampton General Hospital, Tremona Road, Southampton	CU	Wiley
United Kingdom	A Controlled, Randomised, Parallel Group, Multicentre Study of the Efficacy and Safety of Herpes Simplex Virus-Thymidine Kinase Gene Therapy (Cerepro?), with Subsequent Ganciclovir, for the Treatment of Patients with Operable High-Grade Glioma	humans	Herpes simplex virus thymidine kinase (HSV-TK)	Herpes simplex virus		CU	Wiley
United Kingdom	Double-blind, randomised, placebo-controlled, parallel group and dose-finding, muticentric, safety and efficacy study with intramuscular injections of NV1FGF in subjects with intermittent claudication	humans	Fibroblast growth factor (FGF)	Naked/Plasmid DNA	Royal Bournemouth hospital	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
United Kingdom	A 2 x 2 Factorial Randomised Phase II Trial Assessing Anti-CEA, Anti-MUC-1 Vaccination +/- Chemotherapy +/- GM-CSF after Surgery in Patients with Stage II Colorectal Cancer	humans	Carcinoembryonic antigen (CEA) MUC-1	Poxvirus + Vaccinia virus		CU	Wiley
United Kingdom	An open, randomised, parallel group study to evaluate the safety, tolerability and immunogenicity of the GW825780 DNA immunotherapeutic when delivered using the PowderJect ND5.5 device to healthy adult volunteer subjects. (EudraCT: 2004-000251-41)	humans	HIV genes	Naked/Plasmid DNA		CU	Wiley
United Kingdom	A randomised efficacy trial of herpes simplex virus HSV1716 in recurrent glioblastoma multiforme	humans	Herpes simplex virus	Herpes simplex virus		CU	Wiley
United Kingdom	Safety and Immunology evaluation of TroVax produced by the Baxter synthetic route in patients with stage IV colorectal carcinoma	humans	Oncofoetal antigen 5T4	Vaccinia virus		CU	Wiley
United Kingdom	A pilot study of lentivirus transduced acute myeloid leukaemia (AML) blasts expressing B7.1 (CD80) and IL-2 for the induction of graft versus leukaemia (GVL) effect in poor prognosis, relapsed AML	humans	Interleukin-2 (IL-2) B7.1 (CD80)	Retrovirus		CU	Wiley
United Kingdom	A phase II exploratory study of the efficacy and safety of OncoVEX GM-CSF in combination with Arimidex in the neoadjuvant treatment of breast cancer in post menopausal women with oestrogen positive tumours	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Herpes simplex virus		CU	Wiley
United Kingdom	A phase I study of adoptive transfer of autologous tumour antigen-specific T cells with pre-conditioning chemotherapy and intravenous IL2 in patients with advanced CEA positive tumours	humans	Carcinoembryonic antigen (CEA) CD3	Retrovirus		CU	Wiley
United Kingdom	A multicentre, randomised, double-blind, placebo-controlled study evaluating the efficacy of BIOBYPASS (ADGVVEGF121.10NH) delivered by NOGA-Gulded/myostar catheter in no options patients with class II-IV angina	humans	Vascular endothelial growth factor (VEGF)	Adenovirus		CU	Wiley
United Kingdom	A phase 2, randomised, double-blind placebo-controlled, parallel group, multicentre, dose-selection study of Ad2/hypoxia inducible factor HIF-1/VP16 in patients with intermittent claudication	humans	Hypoxia inducible factor (HIF)-1alpha/VP16	Adenovirus		CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
United Kingdom	A phase II study of NY-ESO-1 ISCOMATRIX? vaccine followed by recombinant fowlpox NY-ESO-1 (rF-NY-ESO-1) or NY-ESO-1 ISCOMATRIX? vaccine alone in patients with high risk resected NY-ESO-1 positive melanoma and prostate cancer. EudraCT: 2004-004991-36	humans	NY-ESO-1	Poxvirus	Churchill Hospital Oxford	CU	Wiley
United Kingdom	A Phase I Trial of Intra-Peritoneal Ad-hTR-NTR and CB 1954, an Adenovirus-Delivered Telomerase-Directed Enzyme-Prodrug Therapy, in Patients with Advanced Intra-Abdominal Cancer	humans	Nitroreductase	Adenovirus	Beatson Laboratories Glasgow	CU	Wiley
United Kingdom	A Phase I Study of Adoptive Transfer of Autologous Tumour Antigen-Specific T Cells with Pre-conditioning Chemotherapy and Intravenous IL2 in Patients with CD19 Positive Malignancy	humans	Vascular endothelial growth factor (VEGF)	Retrovirus	Christie Research centre Manchester	CU	Wiley
United Kingdom	Safety, Immunology And Efficacy Evaluation Of Trovax In Patients With Stage IV Clear Cell Renal Carcinoma (TV2). EudraCT: 2005-000088-24	humans	Oncofoetal antigen 5T4	Vaccinia virus	Christie Research centre Manchester	CU	Wiley
United Kingdom	An exploratory study of the safety and biological activity of OncoVexGM-CSF in combination with radiotherapy and cisplatin in the treatment of locally advance epithelial cancer of the head and neck. EudraCT: 2005-000777-21	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)		Royal Marsden Hospital London	CU	Wiley
United Kingdom	A multicenter, randomised, double blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of BHT-3009 when administered intramuscularly to patients with relapsing remitting multiple sclerosis (Protocol No. BHT-3009-03). EudraCT: 2005-001340-22	humans	Myelin Basic Protein (hMBP)	Naked/Plasmid DNA	Guy's King's and St Thomas School of Medicine London	CU	Wiley
United Kingdom	An open-labelled, international, multicenter, dose escalating, phase I/II Study of SPC2996, an LNA antisense molecule against Bcl-2, in patients with relapsed or refractory Chronic Lymphocytic Leukaemia EudraCT: 2004-004741-17	humans	Tumor suppressor	Naked/Plasmid DNA	Christie Hospital NHS trust Manchester	CU	Wiley
United Kingdom	A PHASE I, DOSE-ESCALATION TRIAL OF JX-594 (THYMIDINE KINASE-DELETED VACCINIA VIRUS ENCODING GM-CSF) ADMINISTERED BY INTRAVENOUS INFUSION IN PATIENTS WITH REFRACTORY SOLID TUMOURS EudraCT: 2005-002015-25	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Vaccinia virus	Radcliffe infirmary Oxford	CU	Wiley

Country	Short description /disease	Treated organism	Transgene	Method of transfer	Institution/Company	CU/ DR	Source
United Kingdom	A Phase II Double Blind, Cross_Over Study to Compare the Safety and Efficacy of 125, 250 and 500 ug/kg Monarsen (EN101) administered to Patients with Myasthenia Gravis. EudraCT: 2005_002740_26	humans	Oligodeoxynucleotide against acetylcholinesterase	Naked/Plasmid DNA	Hope Hospital Salford	CU	Wiley
United Kingdom	A Phase III Randomised, Open-Label Study of Docetaxel in Combination with CG1940 and CG8711 versus Docetaxel and Prednisone in Taxane-Naïve Patients with Metastatic Hormone-Refractory Prostate Cancer With Pain. EudraCT: 2005-003275-20	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Adeno-associated virus	Royal Marsden Hospital London	CU	Wiley
United Kingdom	A Phase III Randomised, Open-Label Study of CG1940 and CG8711 Versus Docetaxel and Prednisone in Patients with Metastatic Hormone-Refractory Prostate Cancer who are Chemotherapy-Naïve. EuraCT: 2005-002738-36	humans	Granulocyte-macrophage colony stimulating factor (GM-CSF)	Adeno-associated virus	Beatson Oncology Centre Glasgow	CU	Wiley
United Kingdom	A double blind, placebo controlled study to evaluate the safety and immunogenicity of escalating doses of a candidate oral immunotherapy (M04NM11, formerly called hepatitis B Candidate 1) in patients who have chronic Hepatitis B infection.	humans		Salmonella enterica	Emergent Europe Ltd	DR	JRC
United Kingdom	Live attenuated vaccine for prevention of travellers' diarrhoea		antigen CS1	E. coli	Acambis Research Ltd	DR	JRC
United Kingdom	Phase I clinical trial of a live attenuated Salmonella typhi vaccine for the prevention of typhoid fever	humans		S. typhi	Acambis Research Ltd	DR	JRC
United Kingdom	An open-label study to determine the safety and immunogenicity of two dose levels (10E8 or 10E9 CFU) of a candidate oral immunotherapy (Hep B Candidate 1) against hepatitis B, given on two occasions, 56 days apart to healthy subjects	humans		Attenuated S. typhi Ty2	Microscience Ltd.	DR	JRC
United Kingdom	synthesis of a vaccine			Attenuated S. typhi Ty2	Microscience Ltd.	DR	JRC
United Kingdom	synthesis of a vaccine			E. coli	Acambis Research Ltd	DR	JRC
United Kingdom	synthesis of a vaccine			S. typhi	Microscience Ltd.	DR	JRC