INTERNATIONAL MEDICAL TOURISM FROM THE NETHERLANDS FOR GENE THERAPY

20 October 2010

Schenkelaars Biotechnology Consultancy
In commission of the Commission on Genetic Modification (COGEM)

CONTENT

SUMMARY

In October 2006 the Commission on Genetic Modification (COGEM) reported to the Netherlands Ministry of Housing, Spatial Planning and the Environment estimates suggesting that by the end of 2006 around 50,000 patients would have been treated with Gendicine; worldwide the first gene therapy product that had been registered by the Chinese authorities for treatment of head and neck cancers in 2003. It was further noticed that medical tourism from the Netherlands to China for gene therapy treatment had began. It could therefore be anticipated that in the future the Netherlands would be increasingly confronted with Chinese gene therapy products.

In October 2009, the COGEM indicated that the scope and nature of medical tourism of patients from the Netherlands who have sought treatment with experimental or registered gene therapy products abroad were not known. The potential risks of the spread of the administered gene therapy products from patients who return from abroad to third persons in the Netherlands were neither known. A study was therefore commissioned to Schenkelaars Biotechnology Consultancy, aimed at resolving two key questions:

1. What is the scope of patients from the Netherlands who have travelled and travel abroad for treatment with experimental or registered (approved) gene therapy products?
2. What has been or is the nature of the treatments with experimental or registered (approved) gene therapy products received by patients from the Netherlands?

In the first phase of the study, an overview was prepared of potential suppliers of experimental and registered gene therapy products in other countries than the Netherlands. In addition, a list was compiled of organisations and associations of patients, medical practitioners and healthcare insurers in the Netherlands. As a result, the first phase yielded a map of the supply and demand side for experimental and registered gene therapy products.

A main finding from the first phase of the study is that inspection services of the Netherlands government for healthcare (Inspectie Gezondheidszorg; IGZ) and the environment (Inspectie Milieuhygiëne; IMH) do not have information on patients from the Netherlands who might have travelled to other countries for treatment with experimental or registered gene therapy products.

In the second phase, the focus of the study was directed particularly at therapies involving Adenovirus, Adeno-Associated Virus, Vaccinia Virus, Newcastle Disease Virus, Reovirus, Vesicular Stomatitis Virus and Seneca Valley Virus. The rationale of this selection was that the use of these (potentially genetically modified) viruses could involve risks to the environment and public health because of their competency to replicate; spread of such viruses from patients treated herewith abroad - through so-called viral shedding in the patients' urine, sputum, faeces, etc.- might therefore pose a risk to family members, friends, medical practitioners and other third parties at home.

In total, 69 different institutions and companies involved in 180 gene therapy clinical trials abroad were approached as potential suppliers of experimental gene therapy products. Taken into account that various institutions and most companies were involved in more than one gene therapy clinical trial, the overall response rate to queries for this study was about 60%. A

large majority of these institutions and companies (83%) had information about possible enrolment of patients from the Netherlands in clinical trials with experimental gene therapy products, which they had conducted.

National authorities for clinical trials and/or Genetically Modified Organisms (GMOs) in Belgium, Germany, Ireland and United Kingdom indicated not to be able to deliver the requested information and regularly referred to another authority or organisation in their country that might be able to provide a response. By contrast, national authorities in Austria, Switzerland and France were able to provide the requested information.

Given the findings from the second phase of the study, it is highly unlikely that over the last ten years more than a few patients from the Netherlands have actually sought treatment with experimental gene therapy products through participation in clinical trials abroad. Several responses from institutions and companies further suggested that it would be unlikely that foreign patients would have been enrolled in clinical gene therapy trials, because that would have seriously complicated post-trial monitoring and follow-up care.

In fact, two cases have been found of patients from the Netherlands who have travelled abroad for an experimental gene therapy treatment. One to the US in 2004 for an adenoviral-mediated gene therapy within a clinical trial; in this case information was made available, indicating no viral shedding from the patient's urine, sputum, faeces, etc.. And, more recently, one to Finland for a treatment with an oncolytic virus outside a clinical trial; in this case no further information was made available on the virus used and the results of monitoring of viral shedding in this patient.

The study further identified the Medical Center Cologne in Germany as a clinic that had also been visited by cancer patients from the Netherlands for a treatment with Newcastle Disease Virus (outside a clinical trial). Their actual number could however not be determined. According to this clinic's website, at least two patients from the Netherlands have received treatments with Newcastle Disease Virus. In these two cases, no detailed information was found on the virus used and the results of monitoring of viral shedding in these patients were also not found.

Moreover, it is highly unlikely that over the last five years more than a few patients from the Netherlands have actually travelled to China for treatment with Gendicine or Oncorine, two gene therapy products that have been approved and registered by the Chinese authorities. Yet, in these few cases, it is not clear whether viral shedding from these patients might have posed a risk to relatives, friends, medical practitioners and other third persons after their return in the Netherlands.

Despite the very limited number of patients from the Netherlands, who have actually sought treatment with experimental or registered gene therapy products abroad, it should be noted that in several of these cases detailed information was provided neither on the nature of the virus used in the treatment, nor on the results of monitoring of viral shedding in the patient's urine, sputum, faeces, etc.. In these cases it is therefore virtually impossible to determine whether viral shedding from these patients might have posed a risk to relatives, friends, medical practitioners and other third persons after their return in the Netherlands.

SAMENVATTING

In oktober 2006 rapporteerde de Commissie Genetische Modificatie (COGEM) aan de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieu (VROM) schattingen, die suggereerden dat eind 2006 ongeveer 50.000 patiënten behandeld zouden zijn met Gendicine; wereldwijd het eerste gentherapie product dat in 2003 door de Chinese autoriteiten werd goedgekeurd en geregistreerd voor de behandeling van hoofd- en nekkanker. Opgemerkt werd dat medisch toerisme vanuit Nederland naar China was begonnen. De verwachting was daarom dat in de toekomst Nederland in toenemende mate geconfronteerd zou worden met Chinese gentherapie producten.

In oktober 2009 gaf de COGEM aan dat de omvang en aard van het medisch toerisme van Nederlandse patiënten die voor een behandeling met experimentele of geregistreerde gentherapie producten naar het buitenland afreizen onbekend waren. Hiernaast waren de mogelijke risico's van de verspreiding van toegediende gentherapie producten vanuit de uit het buitenland teruggekeerde patiënten naar derden in Nederland eveneens niet bekend. Aan Schenkelaars Biotechnology Consultancy is toen de opdracht verstrekt om een studie uit te voeren, die gericht was op het oplossen van de volgende twee vragen:

1. Wat is het aantal patiënten die vanuit Nederland naar het buitenland zijn afgereisd voor een behandeling met een experimenteel of geregistreerd (toegelaten) gentherapie product?
2. Wat is de aard van de behandelingen met experimentele of geregistreerde gentherapie producten, die patiënten uit Nederland hebben ondergaan?

In de eerste fase van de studie is een overzicht opgesteld van mogelijke toeleveraars van experimentele en geregistreerde gentherapie producten in andere landen dan Nederland. Hiernaast werd een lijst opgesteld van organisaties van patiënten, medische beoefenaars en ziektekostenverzekeraars in Nederland. Het resultaat van deze eerste fase was een kaart van de aanbod- en vraagzijde voor experimentele en geregistreerde gentherapie producten.

Een belangrijke bevinding van de eerste fase is dat de Inspectie Gezondheidszorg (IGZ) en de Inspectie Milieuhygiëne (IMH) geen informatie hebben over patiënten die mogelijkerwijs naar andere landen zijn afgereisd voor een behandeling met experimentele of geregistreerde gentherapie producten.

In de tweede fase werd de focus van de studie specifiek gericht op therapieën waarbij Adenovirus, Adeno-Associated Virus, Vaccinia Virus, Newcastle Disease Virus, Reovirus, Vesicular Stomatitis Virus en Seneca Valley Virus worden toegepast. De reden voor deze selectie was dat het gebruik van deze (mogelijk genetisch gemodificeerde) virussen tot risico's voor het milieu en de gezondheid zou kunnen leiden; verspreiding van zulke virussen vanuit hiermee in het buitenland behandelde patiënten – door middel van zogeheten 'viral shedding' in de urine, speeksel, uitwerpselen, etc. van de patiënten – kan na hun terugkeer een risico inhouden voor familieleden, vrienden, medische beoefenaars en andere personen in Nederland.

In totaal werden 69 instellingen en bedrijven benaderd, die samen bij 180 klinische gentherapie proeven in het buitenland betrokken waren. Rekening houdend met het feit dat verschillende instellingen en bedrijven bij meer dan één klinische gentherapie proef betrokken waren, bedroeg het aandeel van instellingen en bedrijven die antwoordden ongeveer 60%. Een

grote meerderheid hiervan (83%) beschikte over informatie over mogelijke deelname van patiënten uit Nederland aan klinische proeven die door hen waren uitgevoerd.

Nationale autoriteiten voor klinische proeven en/of genetisch gemodificeerde organismen (ggo's) in België, Duitsland, Ierland en het Verenigd Koninkrijk gaven aan niet in staat te zijn om de gevraagde informatie te leveren en verwezen regelmatig naar een andere autoriteit of organisatie in hun land, die misschien wel in staat zou zijn om te antwoorden. Nationale autoriteiten in Frankrijk, Oostenrijk en Zwitserland daarentegen waren wel in staat om de gevraagde informatie te leveren.

Gegeven de bevindingen van de tweede fase van de studie is het hoogst onwaarschijnlijk dat de laatste tien jaar meer dan een paar patiënten uit Nederland naar het buitenland zijn afgereisd voor behandeling met een experimenteel gentherapie product door deelname aan klinische proeven. Verschillende antwoorden van instellingen en bedrijven suggereerden bovendien dat deelname van buitenlandse patiënten aan klinische proeven onwaarschijnlijk is, omdat dit het volgen en verzorgen van dergelijke patiënten na afloop van de proef ernstig zou bemoeilijken.

In feite zijn er twee gevallen gevonden van patiënten die vanuit Nederland naar het buitenland zijn afgereisd voor een behandeling met een experimenteel gentherapie product. Eén naar de VS in 2004 voor deelname aan een klinische proef met een gentherapie product dat op Adenovirus gebaseerd was; in dit geval werd informatie beschikbaar gesteld, waaruit de afwezigheid van 'viral shedding' in de urine, speeksel, uitwerpselen etc. van de patiënt bleek. En, meer recent, één naar Finland voor een behandeling met een oncolytisch virus buiten een klinisch proef; in dit geval werd geen nadere informatie verstrekt over het gebruikte virus en de resultaten van het monitoren van 'viral shedding' in de patiënt.

Verder identificeerde de studie het Medical Center Cologne in Duitsland als een kliniek die ook bezocht werd door (kanker) patiënten uit Nederland voor een behandeling met Newcastle Disease Virus (buiten een klinische studie). Het feitelijke aantal kon echter niet worden vastgesteld. Volgens de website van de kliniek hebben tenminste twee patiënten uit Nederland behandelingen met Newcastle Disease Virus ondergaan. In deze twee gevallen werd geen gedetailleerde informatie aangetroffen over het gebruikte virus en de resultaten van het monitoren van 'viral shedding' in deze patiënten.

Hiernaast is het hoogst onwaarschijnlijk dat de laatste vijf jaar meer dan een paar patiënten uit Nederland naar China zijn afgereisd voor een behandeling met Gendicine of Oncorine, twee gentherapie producten die door de Chinese autoriteiten zijn toegelaten en geregistreerd. Toch is in deze paar gevallen onduidelijk of 'viral shedding' vanuit deze patiënten na hun terugkeer in Nederland gezorgd heeft voor een mogelijke risico voor familieleden, medische beoefenaars en anderen.

Ondanks het zeer beperkte aantal patiënten, dat vanuit Nederland naar het buitenland is afgereisd voor een behandeling met experimentele of geregistreerde gentherapie producten, moet worden opgemerkt dat in verschillende van deze gevallen er geen gedetailleerde informatie werd verstrekt over de aard van de gebruikte virussen en de resultaten van het monitoren van 'viral shedding' in de urine, speeksel, uitwerpselen, etc. van de patiënten. In deze gevallen is het vrijwel onmogelijk om te bepalen of 'viral shedding' vanuit deze patiënten gezorgd heeft voor een mogelijke risico voor familieleden, medische beoefenaars en anderen.

1. INTRODUCTION

In October 2006 the Netherlands Commission on Genetic Modification (COGEM) reported to the Ministry of Housing, Spatial Planning and the Environment estimates suggesting that by the end of 2006 around 50,000 patients would have been treated with Gendicine; worldwide the first gene therapy product that had been registered by the Chinese authorities for treatment of head and neck cancers in 2003. It was further noticed that medical tourism from the Netherlands to China for gene therapy treatment had began. It could therefore be anticipated that in the future the Netherlands would be increasingly confronted with Chinese gene therapy products.

In October 2009, the COGEM indicated that the scope and nature of medical tourism of patients from the Netherlands who have sought treatment with experimental or registered gene therapy products abroad were not known. The potential risks of the spread of the administered gene therapy products from patients who return from abroad to third persons in the Netherlands were neither known. A study was therefore commissioned to Schenkelaars Biotechnology Consultancy, aimed at resolving two key questions:

3. What is the scope of patients from the Netherlands who have travelled and travel abroad for treatment with experimental or registered (approved) gene therapy products?
4. What has been or is the nature of the treatments with experimental or registered (approved) gene therapy products received by patients from the Netherlands?

In the first phase of the study, an overview was prepared of potential suppliers of experimental and registered gene therapy products in other countries than the Netherlands. In addition, a list was compiled of organisations and associations of patients, medical practitioners and healthcare insurers in the Netherlands. As a result, the first phase yielded a map of the supply and demand side for experimental and registered gene therapy products. For the second phase of the study, both overviews were potential sources of information on patients from the Netherlands who might have travelled abroad for participation in clinical trials with experimental gene therapy products or treatments with registered gene therapy products.

In the second phase, the focus of the study was directed particularly at therapies involving Adenovirus, Adeno-Associated Virus, Vaccinia Virus, Newcastle Disease Virus, Reovirus, Vesicular Stomatitis Virus and Seneca Valley Virus. The rationale of this selection was that the use of these (potentially genetically modified) viruses could involve risks to the environment and public health because of their competency to replicate; spread of such viruses from patients treated herewith abroad - through so-called viral shedding in the patients' urine, sputum, faeces, etc.- might therefore pose a risk to family members, friends, medical practitioners and other third parties at home. As a result, the second phase yielded information on the scope and nature of international medical tourism from the Netherlands for treatment with experimental or registered gene therapy products abroad.

The findings from the first and second phase of the study are represented in the following sections of this report.

The study has further benefitted from feedback and insights from the COGEM Steering Committee that comprised the following members:

- Rob Hoeben (Leiden University Medical Centre; chair)
- Ben Berkhout (Academic Medical Centre University of Amsterdam)
- Eric van den Akker (GMO Office of National Institute for Public Health and the Environment; RIVM)
- Winald Gerritsen (Free University Medical Centre)
- Marcella Hallemeesch (Netherlands Organisation for Health Research and Development; ZonMw)
- Ruth Mampuys (COGEM)

It should be noted that the quality and reliability of the information compiled for this study and its conclusions are the sole responsibility of the author. It should also be noted that this study report does not represent views of the COGEM in any way.

Wageningen, 20 October 2010

Piet Schenkelaars

2. SUPPLY SIDE FOR GENE THERAPIES

Patients may seek access to treatments with experimental or registered gene therapy products in different ways. This section will therefore map these different ways, starting with a general description of clinical trials and other uses of experimental or registered drugs. Then, a worldwide overview of clinical trials with experimental gene therapy products is presented. This sections closes with an overview of gene therapy products that are approved and registered or near commercialisation.

2.1 Clinical trials and other uses of experimental and registered drugs

Although there are many definitions of clinical trials, they are generally considered to be biomedical or health-related research studies in human beings that follow a pre-defined protocol. Participants in clinical trials can gain access to new treatments before they are widely available, and help others by contributing to medical research. All clinical trials have guidelines about who can participate. Using inclusion and exclusion criteria is an important principle of medical research that helps to produce reliable results. The factors that allow someone to participate in a clinical trial are called "inclusion criteria" and those that disallow someone from participating are called "exclusion criteria". These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. Before joining a clinical trial, a participant must qualify for the study. Some research studies seek participants with illnesses or conditions to be studied in the clinical trial, while others need healthy participants. It is important to note that inclusion and exclusion criteria are not used to reject people personally. Instead, the criteria are used to identify appropriate participants and to perform a safe study. The criteria help ensure that researchers will be able to answer the questions they plan to study.

Clinical trials are conducted in phases. The trials at each phase have a different purpose and help scientists answer different questions:

1. In Phase I trials, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
2. In Phase II trials, the experimental study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.
3. In Phase III trials, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.
4. In Phase IV trials, post marketing studies collect additional information including the drug's risks, benefits, and optimal use.

Clinical trials are thus one of the options for patients to gain access to experimental drugs or therapies. However, under certain circumstances, experimental drugs or therapies may also be used outside clinical studies to treat patients who cannot participate in such clinical trials. In case of a registered drug, patients may be treated with that drug for the conditions it was clinically tested and registered. But patients may also be treated with a registered drug for conditions that are beyond the conditions for which the use of the drug was registered. While information about clinical trials can in principle be accessed at various (governmental)

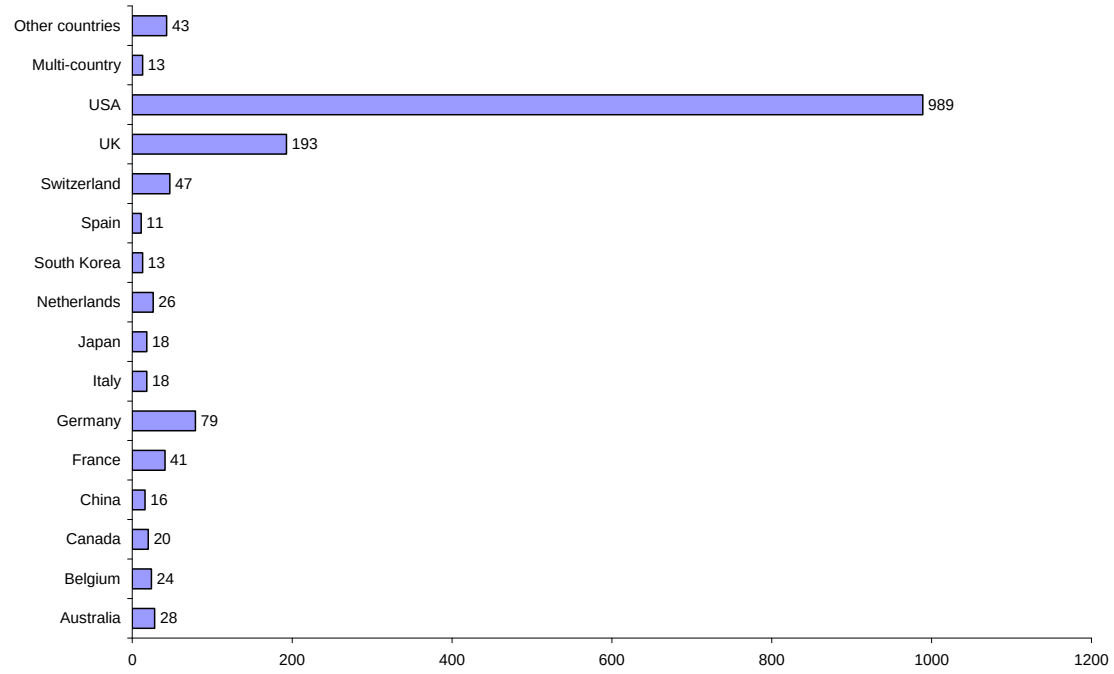
databases, information about possible uses of experimental drugs outside clinical studies or uses of registered drugs are very difficult to access.

2.2 Overview of gene therapy clinical trials

Geographical distribution of gene therapy clinical trials

So far, over 1547 gene therapy clinical trials have been completed, are ongoing or have been registered worldwide, according to the data base maintained by The Journal of Gene Medicine[1]. As of March 2010, entries on 1534 trials in 28 different countries have been retrieved as well as 13 multi-country trials. Since the last review in 2007 (Edelstein et al. 2007) 157 new entries of gene therapy clinical trials have been stored in this database; 116 in 2008, 40 in 2009 and 1 in 2010. The overwhelming majority of the completed, ongoing or approved gene therapy clinical trials (1010) has been conducted in the United States, followed by Europe with 476 of such trials, while in Asia over 58 gene therapy clinical trials have been conducted See Figure 2.1. for the geographical distribution of gene therapy clinical trials by country.

Figure 2.1: Geographical distribution gene therapy clinical trials by country



Source: The Wiley-database (accessed March 2010)

Conditions targeted with gene therapy

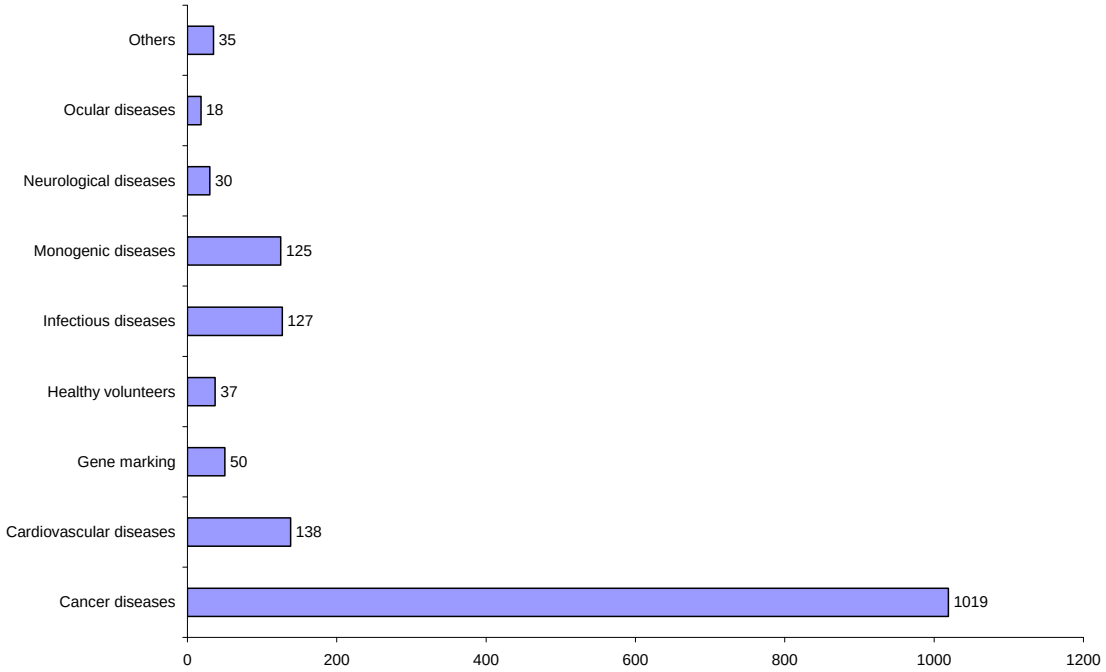
Almost two-thirds of all gene therapy clinical trials have been targeted against cancer. Cardiovascular diseases, infectious diseases and monogenic diseases have each been the target of about ten percent of all gene therapy clinical trials. In addition, a limited number of

[1] http://www.wiley.co.uk/genmed/clinical/

gene therapy clinical trials has been targeted against neurological, ocular and other diseases (see Figure 2.2 for the indications addressed by gene therapy clinical trials).

The vast majority (more than 80%) of gene therapy clinical trials have addressed cancer, cardiovascular diseases and inherited monogenic disorders. According to Edelstein et al. (2007), the first two because of their enormous prevalence, impact and potentially fatal outcomes, the third because the concept of substituting a well-defined defective gene with its correctly functioning counterpart has an obvious appeal and rationale. It was further noted that trials targeting cardiovascular diseases have outnumbered trials for monogenic disorders since 2004, although the greatest successes so far of gene therapy has been achieved in the latter group. Table 2.1 shows the indications for which gene therapy trials have been approved.

Figure 2.2: Indications addressed by gene therapy clinical trials 1989 - 2009



Source: The Wiley-database (accessed March 2010)

In the case of gene therapy trials targeting cancer, a range of different strategies has been applied, including:

- Delivery of the wild-type P53 tumour-suppressor gene and its expression has been shown to cause regression of established human tumours or to prevent growth of human cancer cells in culture. Some clinical trials using the P53 gene have been combined with standard chemotherapy and radiotherapy.
- Immunotherapy of cancer aims to control or eradicate tumours by intensifying the normally weak humoral and/or cellular reactions to tumour antigens in tumour-bearing hosts. Strategies deployed included vaccination with tumour cells engineered to express immunostimulatory molecules, vaccination with recombinant viral vectors encoding tumour antigens, vaccination with dendritic cells expressing tumour antigens or tumour-derived RNA, naked DNA vaccines and intra-tumoral injection of vectors encoding cytokines or major histocompatibility molecules.

- The gene-directed enzyme production therapy (GDEPT) approach consists of the targeted introduction or expression of genes that encode enzymes (often termed 'suicide genes') capable of converting pro-drugs into cytotoxic drugs where needed. The GDEPT approach enables better utilisation of conventional chemotherapy. Most commonly, herpes simplex virus (HSV) thymidine kinase is used to convert the non-toxic pro-drug ganciclovir into cytotoxic triphosphate ganciclovir.

Table 2.1: Conditions for which human gene transfer trials have been approved

Monogenic disorders	**Cancer**	**Neurological diseases**
Cystic fibrosis	*Gynaecological*	Alzheimer's disease
Severe combined immunodeficiency (SCID)	- Breast, ovary, cervix	Carpal tunnel syndrome
Alpha-1 antitrypsin deficiency	*Nervous system*	Cubital tunnel syndrome
Haemophilia A and B	- Glioblastoma, leptomenigeal carcinomatosis, glioma, astrocytoma, neuroblastoma	Diabetic neuropathy
Hurler syndrome	*Gastrointestinal*	Epilepsy
Hunter syndrome	- Colon, colorectal, liver metastases, post-hepatitis liver cancer, pancreas	Multiple sclerosis
Huntington's chorea	*Genitourinary*	Myastenia gravis
Duchenne muscular dystrophy	- Prostate, renal	Parkinson's disease
Becker muscular dystrophy	*Skin*	Peripheral neuropathy
Canavan disease	- Melanoma	
Chronic granulomatous disease (CGD)	*Head and neck*	**Cardiovascular diseases**
Familial hypercholesterolaemia	- Nasopharyngeal carcinoma	Peripheral vascular disease
Gaucher disease	*Lung*	Intermittent claudication
Fanconi's disease	- Adenocarcinoma, small cell, non small cell	Critical limb ischemia
Purine nucleoside phosphorylase deficiency	*Mesothelioma*	Myocardial ischemia
Ornithine transcarbamylase deficiency	*Haemotological*	Coronary artery stenosis
Leukocyte adherence deficiency	- Leukaemia, lymphoma, multiple myeloma	Stable and unstable angina
Gyrate atrophy	*Sarcoma*	Venous ulcers
Fabry disease	*Germ cell*	Vascular complication of diabetes
Familial amyotrophic lateral sclerosis		Pulmonary hypertension
Junctional epidermolysis bullosa	**Infectious diseases**	Heart failure
Wiskott-Aldrich syndrome	HIV/AIDS	
Lipoprotein lipase deficiency	Tetanus	**Other diseases**
Late infantile neuronal ceroid lipofuscinosis	Epstein-Barr virus	Inflammatory bowel disease
RPE65 mutation (retinal disease)	Cytomegalovirus infection	Rheumatoid arthritis
Mucopolysaccharidosis	Adenovirus infection	Chronic renal disease
	Japanese encephalitis	Fractures
Ocular diseases	Hepatitis C	Erectile dysfunction
Age-related macular degeneration	Hepatitis B	Anaemia of end stage renal disease
Diabetic macular edema	Influenza	Parotid salivary hypofunction
Glaucoma		Type I diabetes
Retinitis pigmentosa		Detrusor overactivity
Superficial corneal opacity		Graft versus host disease

Source: Edelstein et al. (2007)

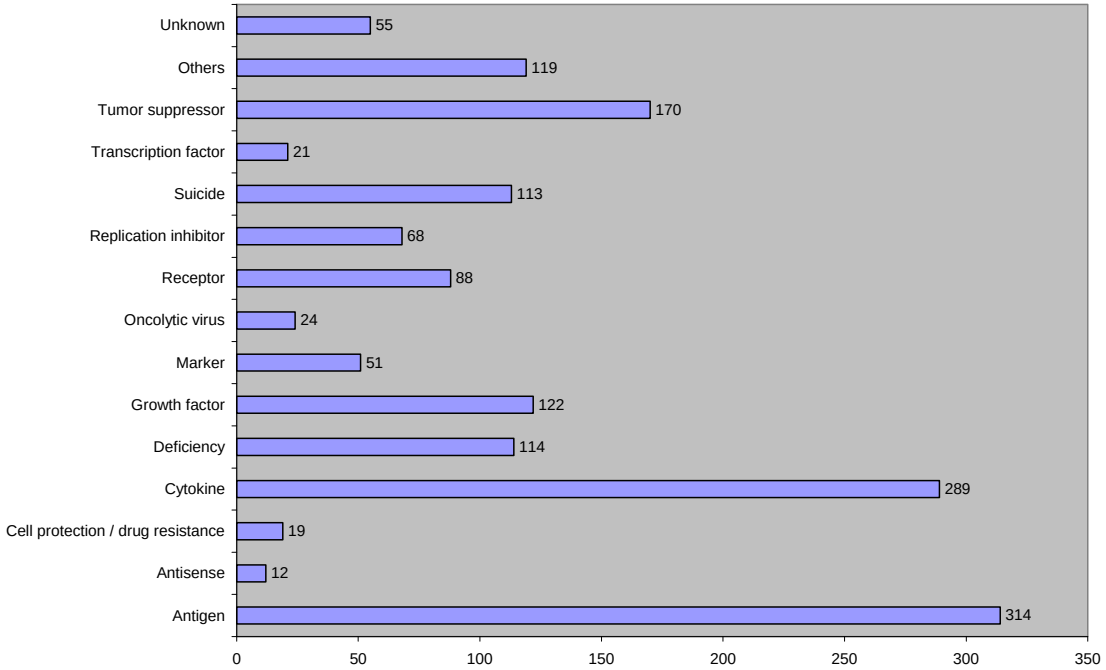
Cardiovascular gene therapy is becoming the second most popular application for gene therapy. It is expected to provide a new avenue for therapeutic angiogenesis, myocardial protection, regeneration and repair, prevention of restenosis flowing angioplasty and prevention of bypass graft failure. The vast majority of these trials have targeted therapeutic angiogenesis to increase blood flow to ischemic regions, like for example in the case of myocardial ischemia due to coronary artery disease and lower limb ischemia due to peripheral artery disease. The fibroblast growth factor (FGF) family and the vascular endothelial growth

factor (VEGF) have been widely applied. Further, the platelet-derived growth factor (PDGF) has been used to treat foot ulcers resulting from the microvascular disease of diabetes, while the hypoxia-induced factor (HIF) has been applied to stimulate angiogenesis.
The first common group of inherited monogenic disorders targeted by gene therapy trials has been cystic fibrosis. The second common group has consisted of severe combined immunodeficiency syndromes for which gene therapy has shown lasting and clinically meaningful therapeutic benefit. Another monogenic immunodeficiency, chronic granulomatous disease, has also been the target of a successful gene therapy trial. Around 20 other monogenic disorders have been treated, though without clear therapeutic benefits yet.
Most of the gene therapy trials performed for infectious diseases have been targeted at infection by HIV or Hepatitis C.
Neurological diseases targeted by gene therapy trials have included multiple sclerosis, myasthenia gravis, neurological complications of diabetes, Alzheimer's disease and Parkinson's disease.
Further, several ocular diseases have been treated with gene therapy, focusing on conditions like retinitis pigmentosa, glaucoma and age-related macular degeneration.
Finally, gene therapy trials have also been conducted for several other diseases, such as inflammatory bowel disease, rheumathoid arthritis, chronic renal disease and fractures.

Therapeutic gene types used in gene therapy clinical trials

Around 60% of the gene therapy trials has applied genes coding for antigens used to stimulate an immune response, cytokine genes, tumour-suppressor genes or suicide genes, in order to combat cancer. Growth factors have been transferred in about 8% of the trials, mostly targeted at cardiovascular diseases. To date, over 220 different genes have been inserted into cells for gene therapy trials. Figure 2.3 provides an overview of the main therapeutic gene types used.

Figure 2.3: Gene types used in gene therapy clinical trials 1989 - 2009

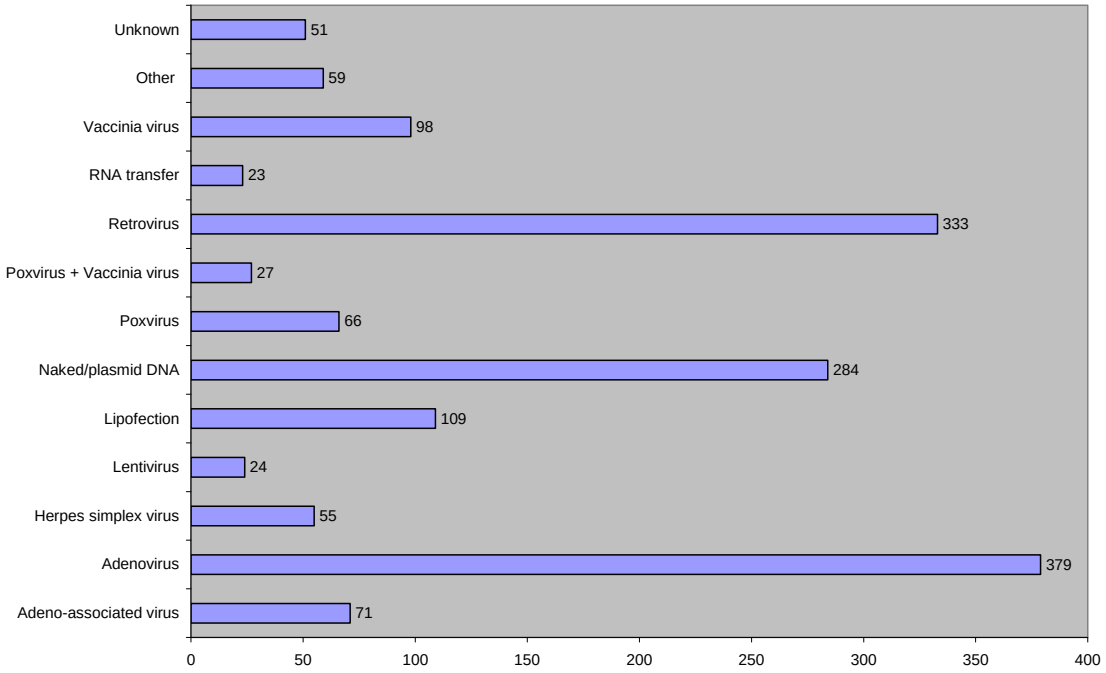


Source: The Wiley-database (accessed March 2010)

Viral vectors used in gene therapy clinical trials

Figure 2.4 shows the wide range of different vectors and delivery techniques that have been used in gene therapy trials. Non-viral approaches have become more common but viral vectors have remained the most popular approach and have been deployed in about two-thirds of all gene therapy trials.

Figure 2.4 Vectors used in gene therapy clinical trials 1989 - 2009



Source: The Wiley-database (accessed March 2010)

In first instance, retroviral vectors have been used most, but due the serious adverse events in the first French gene therapy trials targeted at SCID their use has decreased. To address the drawback of their use, retroviral vectors are engineered into Self Inactivating (SIN) retroviral vectors, in order to minimise the risk that replication-competent retrovirus will emerge and of insertional mutagenesis.

To date, adenoviruses are the most commonly used vectors in almost one quarter of all gene therapy trials. Adenoviruses can carry a larger DNA fragment than retroviruses but their capacity is still too small to accommodate the genes required for certain clinical applications. The main advantage of adenoviral vectors are their high efficiency of transduction and high level of gene expression, though this is transient and declines rather rapidly. There are however important patient's safety issues involved in the deployment of adenoviral vectors, as they may provoke a severe immune and inflammatory response.

Other viruses have been less widely used as vectors for gene delivery and include vaccinia virus, poxvirus, adeno-associated virus and herpes simplex virus. Their use has increased significantly as alternatives to retroviral vectors, for instance through improved capacity.

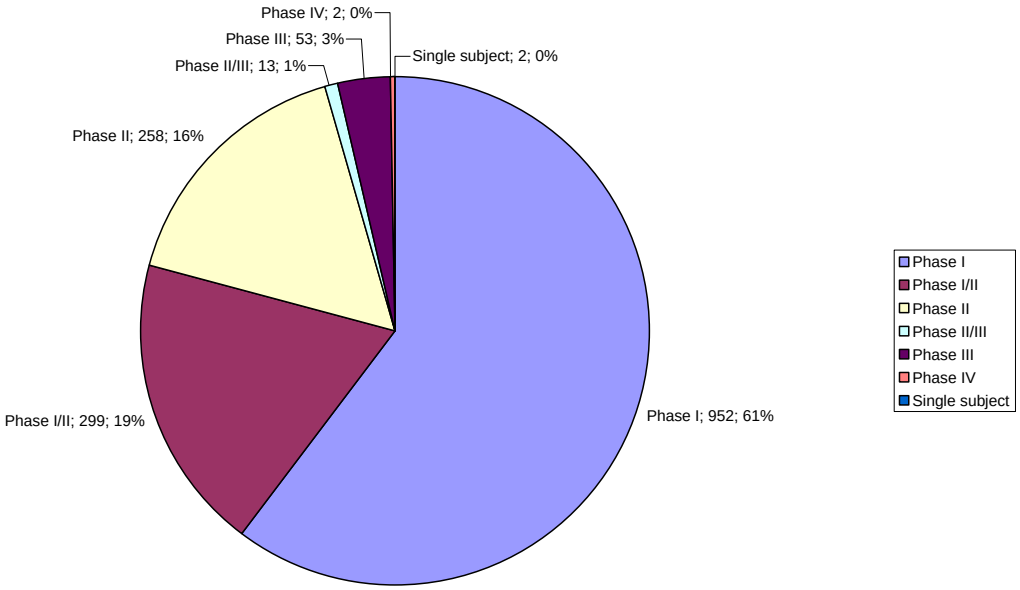
The limitations of viral vectors and patient's safety concerns have led to the development of synthetic vectors not based on viral systems. The simplest non-viral gene-delivery system uses 'naked DNA'. When injected directly into certain tissues, particularly muscle, 'naked DNA' leads to substantial levels of gene expression, though lower than those achieved with viral vectors. Another popular non-viral delivery system is lipofection, which involves cationic lipid-DNA complexes.

Phases of gene therapy clinical trials

As Figure 2.5 shows, the majority of gene therapy clinical trials are Phase I or Phase I/II. Together, they account for 80% of all gene therapy clinical trials, whereas Phase II/III and III gene therapy clinical trials account for about 4% of all trials.

Compared to findings by Edelstein et al. in 2007, when Phase II, II/III and III represented 19% of all trials, in 2009 these trials accounted for 20% of all trials; an indication that gene therapy is still slowly moving closer to clinical applications.

Figure 2.5 Phases of gene therapy clinical trials



Source: The Wiley-database (accessed March 2010)

2.3 Other data sources for gene therapy clinical trials

The overview of gene therapy clinical trials in the previous paragraph is based on the so-called Wiley database, which is maintained by The Journal of Gene Medicine. There are however several other databases, such as those localised and accessed at GeneTherapyNet (www.genetherapynet.com).[2] Some of these databases contain information on clinical trials in general, of which gene therapy clinical trials constitute a subset, while others have been set up specifically for making information on gene therapy publicly accessible. Moreover, some of these databases provide detailed contact information about the principal investigator or lead institution, while others do not. In addition, regulatory frameworks for (advanced) (gene)

[2] Examples include: 1) Belgian Biosafety Server – Clinical data on approved gene therapy trials in Belgium; http://www.biosafety.be/GT/Regulatory/Table_2.html; 2) DeReG – Germany Registry for Somatic Gene-Transfer Trials; http://www.dereg.de/dereg_new/dereg_extern/index.faces; 3) GeMCRIS – Genetic Modification Clinical Research Information System (US National Institute of Health; http://www.gemcris.od.nih.gov/Contents/GC_HOME.asp; 4) World Health Organisation International Clinical Trials Registry Platform (WHO – ICTRP); http://www.dereg.de/dereg_new/dereg_extern/index.faces

(therapy) clinical trials and regulatory definitions of 'gene therapy' differ from one country to another country.

For example, in some EU member states gene therapy clinical trials are considered 'contained use', whereas in other member states they are classified as 'deliberate release' and this classification may, within a member state, also depend on the nature of the gene therapy product. Some authorities indicate that the fact that a human patient is free to leave the hospital is in itself sufficient reasons to consider the trial as a deliberate release (Perseus 2006). Because of differences between provisions on public information between the directive on deliberate release and the directive on contained use, the European Commission Joint Research Centre GMO Website[3] 'only' contains information on gene therapy clinical trials in countries, such as Belgium, the Netherlands, Slovenia, Spain, Sweden and the United Kingdom, which classify (certain) gene therapy trials under deliberate release, whereas the Wiley databases also contains information on gene therapy clinical trials in other EU member states, like Austria, Denmark, Finland, Germany, Italy and Poland.

Notably, a position paper of 2008 the WHO Registry Platform Working Group on the Reporting of Findings of Clinical Trials argues that the value of registration goes far beyond the administrative benefits of having a complete collection of all trials (Ghersi et al. 2008). Registers of clinical trials can have added value, if they:

- Facilitate patient recruitment into clinical trials by raising awareness of their existence among potential participants and health care practitioners;
- Lead to more ethical and successful research by avoiding unintentional duplication of research already under way elsewhere;
- Enhance transparency, making it clear which trials are being conducted so that people can anticipate their results.

According to this position paper, the traditional access to trial results through publication in a peer-reviewed journal has its limitations, particularly where the end users of research information now include healthcare policy-makers, consumers, regulators and legislators who want rapid access to high quality information in a 'user-friendly' format; the Internet is suggested as the main means by which this could be achieved.

Given the background of this study, it should be noted that the search on the Internet for information on gene therapy clinical trials yielded much relevant information, albeit not always in a very user-friendly manner. Moreover, as discussed above, the search was also confronted with differences between formats of various international and national databases on (gene therapy) clinical trials and between (regulatory) definitions as well as differences between the level of detail of the information disclosed.

2.4 Institutions and biotech companies involved in gene therapy

In March 2010 the GeneTherapyNet database contained entries on 13 research institutions in the US and Canada, 6 research institutions in Europe, 7 European Community research projects and 2 research institutions in Australia. It further listed 17 gene therapy societies from Australia, Austria, Finland, France Germany, Ireland, Israel, Japan, South Korea,

[3] http://gmoinfo.jrc.ec.europa.eu/gmo_browse.aspx

Netherlands, Spain, Sweden, Turkey and Europe, and more than 40 biotech companies dedicated to gene therapy product development.

Entries on major international pharmaceutical companies, such as Sanofi-Aventis (Schering-Plough) and Bayer, that might be active in gene therapy product development were not retrieved from GeneTherapyNet, although searches in other databases[4] did yield information on involvement of these companies in gene therapy research and development.

2.5 Biotech companies' pipelines of gene therapy products

In 2005 the deputy head for safety and efficacy sector of the European Medicines Agency (EMA) started seeing the big twenty pharmaceutical corporations making investments in gene therapy; a clear indicator that the field is gathering steam (Osborne 2008). One of the ways of their involvement in gene therapy has been starting collaboration with small (start-up) biotech companies with gene therapy products that have passed pre-clinical stages. Consequently, complicated networks and alliances of established international pharmaceutical firms and biotech companies dedicated to gene therapy product development and commercialisation have evolved over the last five years. Yet, despite all research and development efforts and hundreds of gene therapy clinical trials on both sides of the Atlantic Ocean, neither the FDA in the USA nor the EMA in the EU has thus far given market approval for a gene therapy product.

Around 2008 there were two gene therapy products with the potential to be registered within a few years by US and EU regulatory authorities:

1. Advexin from Introgen (US) and its European subsidiary Gendux Molecular, and;
2. Cerepro from Ark Therapeuticals (Finland/UK).

Advexin developed by Introgen is an adenoviral vector carrying the p53 tumour suppressor gene targeted against Li Fraumeni Syndrome. However, in December 2008 the FDA considered the company's marketing application incomplete. This also led Introgen's European subsidiary Gendux Molecular to withdraw the application for a EU market authorisation.

Further, in December 2009 the EMA rejected the market application of Ark Therapeutics for its adenoviral gene therapy Cerepro targeted against malignant melanoma (Mitchell 2010). According to the EMA, Phase III clinical data did not prove Cerepro's efficacy in terms of postponing death or re-intervention, while it was found associated with an increased risk of serious side effects such as one sided paralysis and seizures (hemiparesis) (EMEA 2009). Ark Therapeutics then announced its discussions with a number of parties that might or might not lead to an offer for the company (Ark Therapeutics 2010).

At present, other examples of biotech companies having pipelines with gene therapy products at advanced clinical development stages include Amsterdam Molecular Therapeutics (Netherlands), Oxford Medica (UK), Telethon (Italy), MolMed (Italy), Généthon (France), Vical (USA) and Targeted Genetics (USA).

[4] See footnote 2.

2.6 Registered gene therapy products

So far, three gene therapy products have been registered for clinical use:

1. Gendicine developed by the Chinese biotech company SiBiono GeneTech was registered by the Chinese State Food and Drug Administration (SFDA) for treatment of head and neck cancer in October 2003 (Edelstein et al. 2007). It is an adenovirus vector carrying the p53 tumour-suppressor gene;

2. In 2005 the Chinese SFDA registered a second gene therapy product developed by Sunway Biotech for treatment of head-and-neck nasopharyngal squamous cell carcinoma (Frew et al. 2008). This product, Oncorine (H101), is an oncolytic adenovirus that targets selectively cells that under-express the tumour suppressor protein p53.

3. Rexin-G developed by the US based company Epeius Biotechnologies received marketing approval for all chemotherapy-resistant solid tumours from the Philippines authorities in December 2007. It consists of replication-defective retroviral vector with a modified cell-cycle control gene, cyclin G, for treatment of metastatic cancers (Bower 2008; Gordon et al. 2009).

3. DEMAND SIDE FOR GENE THERAPIES

This section starts with a short discussion of 'medical tourism' as an emerging trend. This will be followed with an overview of Dutch organisations and associations of patients, medical practitioners and healthcare insurers as potential sources of information on Dutch patients who might have travelled abroad seeking treatment with experimental or registered gene therapy products. This section closes with a brief examination of the information available at Dutch regulatory authorities and inspection agencies.

3.1 Medical tourism

Patients of many countries have long travelled to the US and Europe to seek the expertise and advanced technologies and treatments available in medical centres. In the recent past, a trend known as medical tourism has emerged, wherein patients of the US and Europe choose to bypass care offered in their own communities and travel to other regions in the world to receive a wide variety of medical services, like cosmetic, cardiac and orthopaedic surgery, dental procedures, organ and cellular transplantation, assisted reproductive technology, ophthalmological care, gender reassignment procedures, health evaluations, rehabilitation, etc. Reasons for this medical tourisms include:

- Low costs of treatments;
- Circumvention of delays associated with long waiting lists at home, and;
- Access to treatments not available at home, such as stem cell therapies and gene therapies.

Since 2006 peer-reviewed medical and health journals started publishing papers on this phenomenon, while healthcare insurers, employers, medical practitioners, specialised medical travel agencies and patients have become active participants in shaping this novel form of medical tourism (Horowitz 2007).

3.2 Dutch associations of patients, medical practitioners and healthcare insurers

- Vereniging Samenwerkende Ouder- en Patiënten Organisaties (VSOP) has about 60 member-organisations, each dedicated to a specific genetics-related condition or disease.

- Nederlandse Patiënten en Consumenten Federatie (NPCF) has about 29 member-organisations, most of them dedicated to a specific condition or disease; VSOP is also one of its members.

- Koninklijke Nederlandse Maatschappij ter bevordering van de Geneeskunde (KNMG) is the Dutch association of medical practitioners. The following associations are associated with KNMG: Landelijke Vereniging van Artsen in Dienstverband (LAD); Landelijke Huisartsen Vereniging (LHV); Orde van Medisch Specialisten; Nederlandse Vereniging voor Arbeids- en Bedrijfsgeneeskunde (NVAB); Nederlandse Vereniging voor Verzekeringsgeneeskunde (NVVG); Academie voor Medisch

Specialisten; Artsen Jeugdgezondheidszorg Nederland (AJN); Nederlands Huisartsen Genootschap (NHG).

- Zorgverzekeraars Nederland (ZN) has 34 healthcare insurers as members.

Besides localising these organisations on the Internet, the search in the first phase of the study also scanned these websites for information on gene therapy and their possible involvement. While on several of these websites news items have been posted about developments in gene therapy, none of these websites provided clues about patients from the Netherlands treated with experimental or registered gene therapy products abroad.

3.3 Governmental inspection services in the Netherlands

Both the inspection service of the Ministry of Public Health (Inspectie Gezondheidszorg, IGZ) and the inspection agency of the Ministry of the Environment (Inspectie Milieuhygiene, IMH) have responsibilities to ensure that activities with gene therapy products are conducted in compliance with regulations on medicines, clinical trials and genetically modified organisms (GMOs). Both these inspection services were approached with the question whether they had information on patients who travelled from the Netherlands, seeking treatment with experimental or registered gene therapy products abroad.

The IGZ first stated in its response that it was based on information obtained from the RIVM, the National Institute for Public Health and Environment, which had indicated to the IGZ that it had no data or information on patients from the Netherlands, who might have sought gene therapy treatment abroad. The IGZ further indicated not to be fully sure whether this would fall within its mandate. In addition, the IGZ suggested that healthcare insurers would probably know how many patients had been treated abroad but it doubted whether healthcare insurers would be prepared to share such information because of privacy reasons.

The IGZ also pointed at the complexity of (regulatory) definitions for ‘gene therapy’, thereby referring to EU Regulation 1397/2007 on advanced therapy medicinal products and Directive 2009/120 (amending Directive 2001/83) which defines gene therapy medicinal products. It was further pointed out that medicines based on a GMO are not necessarily to be considered ‘gene therapy’ and, therefore the question was raised what is meant by ‘gene therapy’ in the context of this study.

The IMH also indicated not to have information about patients from the Netherlands, who might have sought gene therapy treatment abroad.

4. RESPONSES FROM THE SUPPLY AND DEMAND SIDE

This section starts by describing how potential suppliers of experimental and registered gene therapy products were selected, identified, approached and responded, followed by an examination of responses provided by several national authorities in seven European countries. Thereafter, the results from approaching organisations of patients, medical practitioners and healthcare insurers in the Netherlands are presented. This section closes with an examination of the findings from case studies on the Docrates Clinic in Helsinki, Finland, the Medical Centre Cologne in Cologne, Germany, and SiBiono and Sunway Biotech, two biotech companies in China.

4.1 Survey method for the supply side

In the first phase of the study, the supply side of experimental and registered gene therapy products had been mapped, indicating two major ways for patients from the Netherlands who may seek access to gene therapy abroad; 1) clinical gene therapy trials, and; 2) treatment with registered gene therapy products, for instance in China, where Gendicine or Oncorine, both based on Adenovirus, have been approved, or the Philippines, where Rexin-G, a retroviral-based gene therapy product, has been approved.

For the second phase, it was decided by the COGEM Steering Committee to focus on therapies based on Adenovirus, Adeno-Associated Virus, Vaccinia Virus, Newcastle Disease Virus, Reovirus, Vesicular Stomatitis Virus and Seneca Valley Virus. The rationale of this selection was that the use of these (potentially genetically modified) viruses could involve risks to the environment and public health because of their competency to replicate; spread of such viruses from patients treated herewith abroad - through so-called viral shedding in the patients' urine, sputum, faeces, etc. - might therefore pose a risk to family members, friends, medical practitioners and other third parties at home.

Against this background, a selection was made of clinical gene therapy trials based on the selected viruses, followed by an identification of the institutions and companies involved in these trials. These institutions and companies were subsequently approached with a request to provide information on whether patients from the Netherlands had been treated with one or more of the selected viruses, and if so, what the nature of the treatment had been. Several national authorities for clinical trials and/or GMOs in Austria, Belgium, Germany, France, Ireland, Switzerland and United Kingdom were also approached with a similar request for information.

Further, a selection was made of hospitals in China, which may treat foreign patients with Gendicine or Oncorine, two registered adenoviral based gene therapy products. These hospitals were subsequently approached with a request to provide information on whether patients from the Netherlands had been treated with Gendicine or Oncorine, and if so, what the nature of the treatment had been. In addition, further information was sought from SiBiono, the company that developed and commercialised Gendicine, and Sunway Biotech, the company that developed and commercialised Oncorine.

Finally, searches on the Internet had also resulted in the identification of two clinics in Europe, which indicated to use one of the selected viruses for treatment of cancer: the

Docrates Clinic (Adenovirus) in Finland and the Medical Center Cologne (Newcastle Disease Virus) in Germany.

Suppliers of selected experimental gene therapy products: The following three data sources and search terms were used:

- ClinicalTrials.gov[5] of the US National Institute of Health using the following search terms:
  - "gene therapy" AND "Adenovirus", leading to 45 studies;
  - "gene therapy" AND "Adeno-Associated Virus", leading to 16 studies;
  - "gene therapy" AND "Vaccinia virus", leading to 1 study;
  - "Reovirus", leading to 9 studies;
  - "Newcastle Disease Virus", leading to 1 study;
  - "Measles Virus", leading to 11 studies;
  - "Vesicular Stomatitis Virus", leading to 0 studies, and;
  - "Seneca Valley Virus", leading to 0 studies.

- GMO.Info[6] of the European Commission Joint Research Centre – Deliberate Releases other than plants, leading to 3 ("Adenovirus") studies and 2 ("Adeno-Asociated Virus") studies in Spain and 4 ("Adeno-Asociated Virus") studies in Sweden.

- Analysis of the applicability of the contained use legislation for clinical trials (Perseus 2006)[7], leading to:
  - Belgium: "Adeno-Associated Virus" (2 studies), "Adenovirus" (15 studies), and "Vaccinia Virus" (8 studies);
  - Finland: "Adenovirus" (3 studies);
  - France: "Adenovirus" (6 studies);
  - Germany: "Adenovirus" (13 studies) and "Vaccinia Virus" (6 studies);
  - Spain: "Adenovirus" (12 studies) and "Vaccinia Virus" (1 study);
  - Sweden: "Adenovirus" (1 study);
  - Switzerland: "Adenovirus" (10 studies), "Adeno-Associated Virus" (1 study) and "Vaccinia Virus" (9 studies);
  - United Kingdom: "Adenovirus' (22 studies), "Adeno-Associated Virus" (2 studies) and "Vaccinia Virus" (15 studies).

These three data sources and search terms eventually led to 69 different research institutions and companies from Australia, China, Finland, Ireland, Spain, Sweden, Switzerland, Turkey, United Kingdom and United States, engaged in 180 clinical gene therapy trials in total. They were subsequently sent one or twice a request for information. In total, responses were received from 42 different research institutions and companies, a response rate of 60%. Of these 42 responses, 7 responses indicated that the research institution or company did not have (access to) information on the nationality of the patients enrolled into a clinical gene therapy trial.

Table 4.1 provides an overview of the numbers of institutions and companies approached and responses received.

[5] http://clinicaltrials.gov/ct2/home
[6] http://gmoinfo.jrc.ec.europa.eu/gmo_browse.aspx
[7] http://ec.europa.eu/environment/biotechnology/pdf/clinical_trial_study_report.pdf

Table 4.1 Responses from institutions and companies

Entity	Number of entities approached	Number of responses received	Response rate	Number of responses with 'information available'	Number of Responses with 'no information available'
Institution	57	35	61%	30	5
Company	12	7	58%	5	2
Total	69	42	60%	35	7

Source: compiled by the author(2010)

Moreover, 11 national authorities for clinical trials and/or GMOs in seven European countries (Austria, Belgium, Germany, France, Ireland, Switzerland and United Kingdom) were also approached. All of them provided a response. Authorities from Austria, France and Switzerland indicated to have information that no patients from the Netherlands had participated in a clinical gene therapy trial in their country. Authorities from Belgium, Germany, Ireland and United Kingdom indicated to have no information on the nationality of the patients enrolled into clinical gene therapy trials in their country.

Suppliers of selected registered gene therapy products: A selection was made of 80 upper-class hospitals with cancer treatment facilities hospitals in Beijing, Shanghai, Tianjin, Guangzhou and Shenzhen, as these cities can be rather easily reached by travellers coming from Europe. These hospitals have been approached twice with a request for information that had been translated into Chinese. Of these 80 hospitals, only the Beijing Great Wall Hospital in Beijing provided a response.
Information was also sought directly from SiBiono and Sunway Biotech. Since no contact details were found on Sunway Biotech's website, only SiBiono was approached with a request for information. Yet, no replies were received from SiBiono. The Dutch Embassy in Beijing was then requested to contact SiBiono and Sunway Biotech but its staff indicated not being able to contact these companies. In both cases additional information was sought through extensive searches on the Internet.

European clinics using one of the selected viruses: The Docatres Clinic in Finland and the Medical Center Cologne in Germany were both approached with a request of information several times. Eventually, only the Docrates Clinic provided a response, whereas the Medical Center Cologne refused to reply to queries, both by email and phone. In both cases additional information was sought through extensive searches on the Internet.

4.2 Summarised responses from institutions, companies and national authorities

This paragraph presents an overview of the summarised responses received from institutions, companies and national authorities.

Austria

- **Austrian Agency for Health and Food Safety**: An enrolment of Dutch citizens in gene therapeutic studies in Austria involving one of the relevant recombinant viruses is highly unlikely.

Belgium

- **UniversiteitsZiekenhuis Leuven**: No Dutch patients have been treated with gene therapy or oncolytic viruses.
- **St Pierre Hospital, Brussels**: You may get in touch with the Biosafety Advisory Council.
- **Biosafety Advisory Council**: If you would like to have an idea about the nationality of the patients the only possible way is to contact the investigator.
- **Federal Agency for Medicines and Health**: I have no access to the personal data of patients involved in a clinical trial and people who do (investigators) will most likely not provide this confidential information.

China

- **Phoenix Cancer Center, Beijing Great Wall Hospital:** Our patients are from over 20 countries, a few from the Netherlands (…) Our doctors use blood test, urine test, CT pictures to make sure that cancer patients are cancer free at the time they leave our hospital. If we determine that cancer patients are cancer free, they should be treated as healthy people as before. We do not think it is necessary to check "shedding" in cancer free people.

Finland

- **Kuopio University Hospital**: In our trials, we have not treated patients from abroad.
- **Virtanen Institute for Molecular Medicine, University of Eastern Finland**: There has not been any patient from the Netherlands treated in our research facility.
- **Docrates Clinic**: We have treated one Dutch patient with an oncolytic virus. I can't tell more because of our confidentiality agreement.

France

- **Commission de Génie Biomoleculaire**, Hopital Cochin Pavillon Baudelcoque: During this period there were no Dutch patients.
- **High Council for Biotechnologies**, Faculté de Médecine, Université Tours: The HCB, which is pursuing the work of the CGB has no ability to collect data on the origin of the patient. The other body dealing with gene therapy trials in France, namely the AFSSAPS, might also not be able to provide such information.

Germany

- **Federal Office of Consumer Protection and Food Safety**: We do not keep record of gene therapy trials in Germany (...) Gene therapy trials are under the responsibility of the Paul-Ehrlich-Institut, Langen (PEI).
- **University of Cologne**: Unfortunately our network has no information about patients form the Netherlands which travelled to Germany for a treatment with gene therapy products in one of our centres.
- **Paul-Ehrlich-Institute**: Our institute is authorising clinical trials with gene therapy medicinal products and GMOs in Germany. The nationality of patients as any other personal information is not to be sent to the Paul-Ehrlich-Institute. Therefore I cannot answer your questions. I am not aware of any other institution in Germany except the sponsors of clinical trials, that might be able to answer.

Ireland

- **Beaumont Hospital, Dublin**: No one from the Netherlands has come to our unit for gene therapy.
- **Irish Medicines Board**: We do not have information on whether Dutch patients come to Ireland for such treatments.

Israel

- **Soroka Medical Center & Ben Gurion University of the Negev**: No Dutch patients have been included in our study.
- **The International Center for Cell Therapy & Cancer Immunotherapy (CTCI), Top Ichilov, the Weizman Center**: No Dutch patients have been treated with Newcastle Disease Virus or any genetically modified agent.
- **Hadassah Medical Organisation, Jerusalem**: The principal investigator of this study notified that there were no patients from the Netherlands.

Sweden

- **Department of Oncology, Radiology and Clinical Immunology, Division of Clinical Immunology, Uppsala University**: In our clinical trials using adenoviral vector gene transfer into cancer patients with urinary bladder cancer, only Swedish patients were treated.
- **Clinical Immunology, Rudbeck Laboratory, Uppsala University Hospital**: No patient from Holland has participated in our programs.
- **Department of Hematology, Lund University Hospital**: Short answer from Lund: Zero!

Switzerland

- **University Hospital Zürich**: We are unable to answer your question.
- **Swiss Expert Committee for Biosafety**: It took us quite a while to get the answers back from all the principle investigators involved in clinical trials with the requested vectors. No Dutch patients were involved in any trial in Switzerland.

Turkey

- **Anadolu Medical Center:** We do not have Dutch patients.

United Kingdom

- **The Christie NHS Foundation Trust**: We have had no Dutch patients treated at The Christie.
- **St James's University Hospital, Leeds**: We are not able to respond as nationality data is not routinely collected from patients recruited into such trials.
- **The Royal Marsden, London**: We have not treated any patients from the Netherlands for treatment of their condition with gene therapy products or (wild-type) viruses.
- **Health and Safety Executive**: We do not hold any information regarding the patients involved in any gene therapy trials in our country. It may be worth contacting either GTAC or MHRA.
- **Medicines and Healthcare products Regulatory Agency**: The MHRA has no knowledge of the actual subjects enrolled into a trial (…).

United States

- **Vanderbilt-Ingram Cancer Center**: No patients from the Netherlands treated in our trials.
- **MD Anderson Cancer Center:** We have treated 90 patients from the Netherlands since 1944. Of those 90 patients, 12 were registered during 2008 and 2009, with 7 diagnosed with malignant disease. Of those 7 patients, 2 had chemotherapy and 5 received second opinions.
- **Mayo Clinic**: We have received several requests from patients in the Netherlands asking for participation in our clinical trials using viral agents. So far, we have not treated a single patient. All of our clinical trials include determination of viral shedding before patients are released from the study.
- **University of Pennsylvania Medical Center**: We have been conducting Phase I clinical trials on adenoviral-mediated gene therapy for malignant pleural mesothelioma and other malignant pleural diseases since 1995. In the past 15 years, we have had only one Dutch patient in our trials, and this was in 2004.
- **The Ohio State University Medical Center**: We have not treated anyone from the Netherlands.
- **The Ohio State University Medical Center and Arthur G. James Cancer Hospital and Richard J. Solove Research Center Columbus, Ohio**: No Dutch patients have come here.
- **Oregon Health & Science University, Portland, Oregon**: We have treated no Dutch patients in any of our studies (gene or stem cell therapies).
- **Neuromuscular Division, Center for Gene Therapy, The Research Institute and Ohio State University**: None of the participants were from the Netherlands.
- **Clinical Research Nurse, University of Massachusetts Medical School, Gene Therapy, Worcester, Massachusetts**: We have not treated any patients from the Netherlands.
- **UT Health Science Center San Antonio, Texas**: No patient from the Netherlands was treated in our facility with an investigational gene therapy product. For now we are focusing on treating patients who are residing in the USA, to ensure we can follow-up these patients closely and assess the efficacy of the therapy which is a key objective of this study.
- **Abramson Cancer Center of the University of Pennsylvania, Philadelphia**: We have not treated any Dutch patients with gene therapy or wild-type viruses.
- **Center for Cellular and Molecular Therapeutics, The Children's Hospital of Philadelphia**: No subjects from the Netherlands have been enrolled in gene therapy studies sponsored by our organization.
- **Gene Therapy Center, University of Florida**: No Dutch patients have been treated.
- **University of Iowa**: No Dutch patients have been treated here using any gene therapy.
- **VA San Diego Healthcare System, Veteran Medical Research Foundation**: In our current gene therapy trial (Ad5.hAC6) we have enrolled no patients with a Dutch nationality. For our previous 4 gene therapy trials in which 450 patients (cumulatively) received Ad5.hFGF4 (the AHENT trials), I cannot answer the question, because I was not provided that kind of information. I rather doubt that we enrolled anyone from the Netherlands.
- **American Society of Gene & Cell Therapy, Milwaukee, Wisconsin**: ASGCT does not have access to the type of information you are requesting. I suggest reaching out to the US Food & Drug Administration for more information.

- **National Eye Institute**: The Office of the Clinical Director searched its files and no records responsive to your request were located.
- **National Heart, Lung, and Blood Institute:** The NHLBI has no records of individuals who participate in those studies and no access to the records on study participants maintained by any of those institutions funded by the NHLBI.
- **National Cancer Institute**: NCI does not receive any information about the nationality of patients entering into NCI-sponsored clinical trials.

Companies

- **Ark Therapeutics:** We do not to have direct contact with patients in clinical trials and we do not have access to the information required to answer the query.
- **Broadvector Limited, Melbourne**: Trial subjects are drawn from existing patients, who have received prior treatments at this clinic - these people are Australian residents. It would be very unlikely for someone coming from overseas to join the trial.
- **Bayer Healthcare**: It is undoable to find out whether Dutch patients have participated in gene therapy clinical trials conducted by Bayer (including merged or acquired companies) abroad. In general there are no Dutch patients involved in clinical trials abroad or, in the case of cancer, very sporadically.
- **Cardium Therapeutics Inc.:** I have no knowledge of persons traveling from the Netherlands to other countries to receive treatment.
- **Ceregene Inc.**: Ceregene is currently running clinical studies in Alzheimer's and Parkinson's disease. The company is not directly involved in the recruiting of or management of the patients directly. All direct patient activities are performed at the major Medicals Schools around the United States that are performing the studies for Ceregene. With that said, we do not believe we have enrolled any patients that do not permanently reside in the United States.
- **Oncolytics Biotech Inc**.: to the best of our knowledge no Dutch patients resident in the Netherlands have been treated in any clinical study with Reolysin.
- **Oxford BioMedica**: No patients from the Netherlands were treated in gene therapy clinical trials.

4.3 Responses from the demand side

Based on the findings from the first phase, the following organisations or associations of patients, medical practitioners and healthcare insurers in the Netherlands were approached with a request for information concerning the two key questions of this study. All organisations of patients and medical practitioners that were approached responded, whereas in the case of healthcare insurers 8 out of 15 responded, including the major association of healthcare insurers in the Netherlands. The responses received from the demand side are presented below.

Patients organisations

- **Nederlandse Patiënten Consumenten Federatie** – NPCF: No information; referred to VSOP.

- **Vereniging Samenwerkende Ouder- en Patiëntenorganisaties** – VSOP: Request for information transmitted to member organisations; additional request for information was posted on internal website **Stichting Diagnose Kanker** but this did not yield any response.

Associations of healthcare practitioners

- **Academie voor Medisch Specialisten** – **AMS**: No information.
- **Orde van Medisch Specialisten** – **OMS**: No information.
- **Koninklijke Nederlandsche Maatschappij ter bevordering van de Geneeskunst – KNMG**: No knowledge of patients who travelled abroad for treatment with gene therapy or (wild-type) virus.
- **Landelijke Huisartsen Vereniging – LHV:** No information; referred to VSOP.
- **Nederlands Huisartsen Genootschap – NHG**: No information; referred to NPCF.
- **Nederlands Oogheelkundig Gezelschap** – **NOG**: No knowledge of patients who travelled abroad for treatment with gene therapy or (wild-type) virus; knowledge of two patients treated with lentiviral-based gene therapy against RPE65 Leber's congenital amaurosis in Moorsfield Eye Hospital in London, UK.
- **Nederlandse Orthopaedische Vereniging – NOV**: No knowledge of patients who travelled abroad for treatment with gene therapy or (wild-type) virus.
- **Nederlandse Vereniging voor Arbeids- en Bedrijfsgeneeskunde – NVAB:** No knowledge of patients who travelled abroad for treatment with gene therapy or (wild-type) virus; referred to LHV.
- **Nederlandse Vereniging voor Kindergeneeskunde – NVK**: No knowledge of patients who travelled abroad for treatment with gene therapy or (wild-type) virus.
- **Nederlandse Vereniging voor Obstetrie en Gynaecologie – NVOG**: No knowledge of patients who travelled abroad for treatment with gene therapy or (wild-type) virus.
- **Nederlandse Vereniging voor Neurologie – NVN**: Request for information placed on internal website but this did not yield any response.
- **Nederlandse Vereniging voor Radiotherapie en Oncologie** – **NVRO**: No knowledge of patients who travelled abroad for treatment with gene therapy or (wild-type) virus.
- **Nederlandse Vereniging voor Pathologie** – **NVP**: No knowledge of patients who travelled abroad for treatment with gene therapy or (wild-type) virus.
- **Nederlandse Vereniging voor Keel-Neus-Oorkunde en Heelkunde van het Hoofd-Halsgebied:** No knowledge of patients who travelled abroad for treatment with gene therapy or (wild-type) virus.

Healthcare insurers

- **Achmea Zorg**: We cannot find such detailed information in our system.
- **Azivo Zorgverzekeraar:** No customers who travelled abroad for treatment with gene therapy or (wild-type) virus.
- **De Friesland Zorgverzekeraar**: No information.
- **De Goudse**: No customers who travelled abroad for treatment with gene therapy or (wild-type) virus.
- **Menzis** – **Anderzorg**: About twelve patients per year visit Dr Gorter's clinic in Cologne, although the numbers of Dutch patients might be declining since a few years. And maybe two patients per year have travelled to China for treatment with gene therapy.
- **ONVZ Zorgverzekeraar**: Knowledge of a few patients who travelled abroad for one of the therapies but no detailed information available because the costs of these treatments are not covered by this insurer.
- **Unive**: No information.
- **Zorgverzekeraars Nederland – healthcare insurance branch organisation** (with 34 members): No information because treatments with (experimental) gene therapy or (wild-type) virus (abroad) are not included in the basic package foreseen by the healthcare insurance law.

In addition, searches on patients forums[8] - with Dutch and English search terms, including "cancer", "patients", "forum", "Gendicine", "gene therapy" AND/OR "China" yielded only a very few postings. Some of these postings, mostly dated between 2006 and 2008, suggested that a patient, often from the US or Australia, had sought treatment with Gendicine in China. The few other postings came from people who had heard of gene therapy or Gendicine in China and wished to know more details, but clear responses to such queries were not found on these forums.

[8] Some examples include:

- http://talkcancer.org/cancer-patients/gendicine-is-gene-dna-miracle-cure-1899594.html http://www.topix.com/forum/health/cancer/TRJ3NR7LVCIT2L8QF/p2
- http://www.inspire.com/groups/bladder-cancer-advocacy-network/discussion/chinas-cancer-drug-gendicine/ http://csn.cancer.org/node/156565
- http://bb.sarcomaalliance.com/cgi-executables/anyboard.cgi/anyboard9/forum?cmd=get&cG=2343533343&zu=3234353334&v=2&gV=0&p=
- http://www.cancercompass.com/message-board/message/all,3270,0.htm?mid=133368
- http://www.kanker-actueel.nl/phpBB3/viewtopic.php?f=2&t=683
- http://fora.diagnosekanker.nl/lotgenoten/viewtopic.php?f=37&t=1406
- http://fora.diagnosekanker.nl/lotgenoten/viewtopic.php?f=57&t=2097
- http://www.kankerpatient.net/viewtopic.php?f=6&t=2784&p=37638&hilit=gentherapie#p37638

4.4 Information on suppliers of selected registered gene therapy products

SiBiono Genetech, China: The first biotech company that commercialised a gene therapy product is SiBiono GeneTech, China (Edelstein et al. 2007). In October 2003, the Peoples Republic of China (PRC) State Food and Drug Administration (SFDA) registered type 5 Adenovirus bearing the human wild-type *p53* gene (Ad-p53) for the treatment of head and neck cancer with intratumoural injection and in combination with chemotherapy. This Ad-p53 is trademarked as Gendicine and has been developed by SiBiono GeneTech founded by Dr Zhaohui Peng in Shenzen, China, in 1998.

There were concerns about the approval among gene therapy researchers elsewhere in the world as to quality of the trials performed and thereby the safety and efficacy of the treatment (Pearson et al. 2004). As of 2007, Phase I and Phase II clinical trial results had only been published in Chinese literature. It seemed that approval had been made on the basis of tumour shrinkage rather than extension of patient lifetime. Despite these concerns, patients have flown to China to undergo therapy. For foreign patients Gendicine treatment may cost US $ 20,000 per two-month course and is not covered by US health insurance (Bloomberg Newsweek 2006; Washington Post 2007). Other reports indicated that the costs of a two-month treatment run about US $ 30,000 (Folkmann 2007). According to the search for this study, the company has initiated three Phase IV trials in 2009. Moreover, a number of clinical studies have been performed with an off-labelled use of Genedicine for testing it against lung cancer, breast cancer, mesothelioma, ands esophageal, hepatocellular, gastric, colorectal and pancreatic carcinomas (Frew et al. 2008; Ma et al. 2008).

In April 2007, after struggles to expand its market for Gendicine, SiBiono was acquired by the NASDAQ-listed Chinese pharmaceutical company Benda Pharmaceutical for US$ 15 million (Benda Pharmaceutical 2007). Prior to Benda's acquisition, SiBiono suffered a net loss of $1.0 million in 2006. Following the acquisition, Benda dramatically enhanced the marketing and distribution of Gendicine. It was anticipated that SiBiono would earn US $5.0 million in net income in 2007 - a 600% immediate improvement.

In 2007 it was reported that SiBiono might have infringed intellectual property rights on Advexin, a gene therapy product similar to Gendicine that was being developed by the US company Introgen Therapeutics. Dr Peng maintained that Gendicine had been developed from published literature without violating any patent. (Washington Post 2007; ChinaBio Today 2007). Whether Introgen Therapeutics has meanwhile filed any patent infringement suits against SiBiono is not known. But this would be very unlikely as Introgen Therapeutics' Advexin failed to get approval from the US FDA in December 2008, which eventually led to the company's bankruptcy.

On 19 May 2008, SiBiono received an official notice from the PRC SFDA in which it mentioned that during the random inspection on 8 April to 10 April 2008, the PRC SFDA discovered several production procedures that did not meet the GMP requirements. Consequently, SiBiono was required to perform necessary improvements in order to fulfil the GMP requirements (Benda Pharmaceutical 2010). On 10 June 10 2008, SiBiono received another official notice from Guangdong Province SFDA with the same demands as stated in the official notice of the PRC SFDA. On 24 November 2008, SiBiono received an official notice from Guangdong Province SFDA with a consent to carry out production on a trial basis, requiring to follow the procedures to apply for GMP Certificate verification.

Eventually, on 14 July 2009, SiBiono obtained the final GMP Certificate from the PRC SFDA, allowing to resume its production and sales.

In March 2010 the Chinese press agency Interfax (2010) reported that SiBiono would soon set up five gene therapy centres overseas but further details were not disclosed.

In March 2006, it was reported that since mid-2004 70 foreign patients from 22 countries had sought Gendicine treatment from Dr Li Dinggang at the Beijing-Haidian Hospital and the Beijing-Yanhua Phoenix Hospital; the only hospitals in China that accepts foreigners (Bloomberg Businessweek 2006).

Searches on the Internet for this study also identified these two hospital groups with the following names: the Great Wall International Cancer Centre Beijing[9] and the Phoenix Cancer Centre Beijing (Gene Therapy Centre, Beijing Haidian Hospital and Beijing Yanhua Phoenix Hospital).[10] The first hospital group indicated to have used gene therapy for successfully curing advanced cancer patients from Turkey, Germany, USA, Canada, Singapore, the Netherlands, the UK and other countries. Since 2004, over 4,500 all conditions' patients have been treated. Its website further presents 16 case studies, including 1 from Turkey, 1 from the US and 3 from the Netherlands (see Table 4.2). The website of the second hospital group did not provide numbers of treatments of patients from abroad. Though, it presented two case studies: one on a Turkish woman with breast cancer and the other one on a Canadian woman with squamous cell carcinoma in the nasal cavity.

Correspondence in June 2010 for this study with the Phoenix Cancer Centre Beijing Great Wall Hospital did not lead to a response with precise numbers of Dutch patients treated: “Our patients come from over 20 countries, a few from the Netherlands”.

Table 4.2 Dutch case studies on website Great Wall International Cancer Centre Beijing China

Colon Cancer - Liver Metastasis Sex: Female Age: 70+ years Diagnosis: Patient complained of metastatic colon cancer in liver and abdominal cavity plus abdominal pain with 3 months of survival expected by her Dutch doctor after surgical exploration of abdominal cavity. Therapy: In July 2006, Combination of gene therapy, anti-angiogenesis therapy, cancer stem cell targeting, mild chemotherapy, CIK-DC immunotherapy and traditional Chinese medicine. Results: One month after treatment, patient's abdominal pain disappeared and serum CEA levels significantly dropped. Two months after the treatment, the liver metastases and all symptoms disappeared with the CEA level dropping to normal. Sixteen months after our treatment the patient is still well.
Liver Cancer - Intrahepatic Metastasis Sex: Male Age: 59 years Diagnosis: Patient had a large liver tumour with metastases and abdominal pain after several unsuccessful chemotherapy regimens in Netherlands. Therapy: In January 2005. Combination of Gene therapy, TACE, CIK-DC immunotherapy and traditional Chinese medicine. Results: After two months of the treatment including interventional therapy, the large tumour became mostly necrotic and shrank. Meanwhile, the enlarged lymph nodes in the groin and abdominal pain disappeared.
Lung Cancer Gender: Female Age: 55 Diagnosis: Lung adenocarcinoma with chest pain. Therapy: Combined therapy of Chemotherapy, Anti-angiogenesis therapy, Gene therapy, CIK-DC immunotherapy. Result: After two months of treatment (June 2007 – July 2007), lung lesion greatly released with all symptoms disappeared,1 tumour disappeared and the other tumour significantly shrank after 2 months treatment.

Source: Great Wall International Cancer Centre Beijing China 2010

[9] See http://genetherapyhospitals.com/index.html
[10] See http://www.phoenixcancercentre.com/

In 2004 Dr Peng from SiBiono projected that by the end of 2006 50,000 patients would have received Gendicine (Guo et al. 2006). However, in November 2006, Science magazine reported that Dr Peng claimed that Gendicine had been given to more than 4,000 patients, of whom 400 were from overseas (Frew et al. 2008). In August 2007, SiBiono indicated that about 6000 patients had been treated, including some 800 from overseas (RSC 2007).

In a presentation at the European Society of Gene and Cell Therapy conference in 2007 (Ma et al. 2008) Dr Peng indicated that more than 7,000 cancer patients, including 500 non-residents in total had received Gendicine. By the end of 2007, Dr Peng expected that 10,000 patients would have received Gendicine**.**

In a press release of 18 September 2007, Benda Pharmaceutical (2007) provided the following numbers of patients treated with Gendicine:

- Total patients treated in 2007 second quarter: 2,000
- Foreign patients treated in 2007 second quarter: 130
- Total patient treated from 2003 to 2007 second quarter: 8,700
- Foreign patients from 2003 to 2007 second quarter: 1,800

Before SiBiono was acquired by Benda Pharmaceutical, it had provided an average of 515 treatments Gendicine treatments per quarter.

In summary, the figures on the numbers of (foreign) patients treated with Gendicine as provided by SiBiono or Benda Pharmaceutical between 2004 and 2007 do not seem to be consistent, while figures for the period from 2007 to 2010 have not been found.

Sunway Biotech, China: In 2005 the SFDA registered a second gene therapy product developed by Sunway Biotech for treatment of head-and-neck nasopharyngal squamous cell carcinoma (Frew et al. 2008). This product, Oncorine (H101), is one of a H100 series of oncolytic adenoviruses that target selectively cells that underexpress the tumour suppressor protein p53. It is also being tested for the treatment of non-small-cell lung cancer in combination with standard chemotherapy. The other products in the company's pipeline, H102 and H103, are further modified to target hepatocellular carcinoma and metastatic cancers and are at an early stage of clinical development. In 2007 the number of treatments with Oncorine was far lower than originally expected by Sunway Biotech. But the company had hope that the international market might boost their sales (Royal Society of Chemistry 2007).

In March 2005 Sunway Biotech purchased a license to develop Onyx-15, a prototype gene therapy equivalent to Oncorine. The therapy had been abandoned by the US-based biotech company Onyx after dissatisfactory Phase II clinical trials.

In October 2007 Sunway Biotech and Genzyme, a major US biotech company, agreed on a cooperation. According to the news posting from the Royal Society of Chemistry (2007), to help launch clinical trials with Onyx-015 in the US. But according to the Genzyme 2007 annual report (Genzyme 2007), to help commercialise Genzyme's experimental gene therapy product Ad2/HIF-1a in China. This gene therapy product targets intermittent claudication, a form of peripheral arterial disease that results in disabling pain or fatigue in the legs, brought on by exercise. A Phase II clinical trial with this gene therapy product was conducted from

February 2005 to March 2010, involving more than 300 patients at 40 US and European medical centres. Genzyme has at least two other gene therapy products in the pipeline: AAV-h AADC-2 for treatment of Parkinson's disease and AAV2-sFLT01 for treatment of neovascular age-related macular degeneration. In 2009 Genzyme further acquired the intellectual property rights from Targeted Genetics that faced near-bankruptcy in and invested, through Genzyme Ventures, in Genetix Pharmaceuticals (McBride 2010). At present, Sanofi-Aventis attempts to acquire Genzyme (Sanofi-Aventis 2010).

Finally, compared to information found on SiBiono and Gendicine, the information found on Sunway Biotech and Oncorine was minimal.

4.5 Docrates Clinic, Finland

In 2006 Docrates Clinic (2010) in Finland was set up with the aim to be the top clinic for cancer treatment in Europe. One of its innovative cancer treatments consists of the use of oncolytic adenoviruses.

The use of oncolytic viruses for cancer treatment by Docrates Clinic follows from research performed by the Cancer Gene Therapy Group (CGTG) of the University of Helsinki since 2002. A presentation by Akseli Hemminki from the CGTG suggest that from November 2007 to 2009 202 treatments with 6 different oncolytic adenoviruses have been provided to 134 patients with refractory solid tumours (Hemminki, 2009). Patients usually receive three treatments with an oncolytic virus. While there is no charge for the virus, the total costs of three treatments amounts to 10,000 € to 15,000 €.

Moreover, in 2007, in partnership with Docrates Hospital, Oncos Therapeutics (2010), which was co-founded by Akseli Hemminki, started another programme, the so-called Advanced Therapy Access Program for cancer patients in whom standard-of-care therapies have failed. In this program, 200 patients representing 18 cancer types have been treated with 9 different oncolytic adenoviruses.

At present, Oncos Therapeutics' lead product is CGTG-102, which is based on the serotype 5 adenovirus modified with Granulocyte Macrophage Colony-stimulating Factor (GM-CSF). In April 2010 Oncos Therapeutics raised 4 million € from HealthCap, a venture capital firm specialised in life sciences. In Oncos Therapeutics' view, the momentum for commercialising oncolytic virus based therapies is building up, thereby pointing at US FDA approvals of Phase II and Phase III clinical trials by companies like BioVex (OncoVex^{GM-CSF}), Jennerex (JX-594; an engineered vaccinia virus armed with GM-CSF), and Viralytics (based on coxsackievirus and echovirus). Moreover, in October 2009, the European Medicines Agency issued formal guidance on oncolytic viruses (EMEA 2009a).

Correspondence for this study with the Docrates Clinic and Akseli Hemminki yielded the response that one patient from the Netherlands had been treated with an oncolytic virus. Further details could not be given because of confidentiality.

4.6 Medical Center Cologne, Germany

The Medical Center Cologne (MCC) was founded by Dr Robert Gorter in Cologne, Germany. It operates according to the so-called Gorter Model or Cologne Model (2010). This model is claimed to be innovative, as it integrates traditional western academic medicine with novel therapies and pays significant attention to all the needs of the patient and the characteristics of the tumour itself. All of these therapies would have a sound scientific basis and sufficient clinical experience to guarantee little to no side effects. Examples of the Gorter Model are the treatments with dendritic cells, adult autologous stem cells, various forms of hyperthermia, thymus peptides, *Viscum album* (mistletoe), orthomolecular medicine, improvement of intestinal flora and Newcastle Disease Virus.

In 2006 a Dutch alternative life-style magazine, Ode, devoted substantial attention to Dr Gorter's career and his view on treating cancers and other illnesses at the MCC (Ode 2006). In 1999 he developed a procedure to cultivate so-called dendritic cells for fighting off cancer cells. In his view, dendritic cell therapy is barely getting off the ground. Since dendritic cells cannot be patented, the pharmaceutical industry would not be interested. Dr Gorter also started using other (non-patentable) approaches for curing cancer, like hyperthermia and, later, oncolytic viruses, like Newcastle Disease Virus. One vaccination with dendritic cells costs 2800 €. Usually several vaccinations are needed. Costs of one hyperthermia treatment are 365 €. According to Dr Gorter, Dutch healthcare insurers, like Achmea, Delta Lloyd, Alianz and Agis, would cover the costs of these treatments. In 2009 the MCC opened an advisory bureau in Cairo, Egypt.

Searches for this study on the Internet with the search term 'Robert Gorter' led to numerous postings on various websites from cancer patients groups as well as Dutch and Belgian organisations against quackery. Moreover, in 2008 the Dutch public broadcasting organisation reported on alternative cancer cures, in which Dr Gorter and his clinic featured prominently (Nova 2008). In this report two Dutch oncologists expressed serious criticism on Dr Gorter's approach to curing cancer.

Further, correspondence with the MCC and Dr Gorter and inquiries by phone for this study did not yield any response to the question how many Dutch patients had been administered Newcastle Disease Virus. Follow-up correspondence for this study with a major Dutch healthcare insurer (with about 2 million customers) suggested that a few years ago the MCC was visited by about 12 Dutch patients per year; this number might have declined over the last years. However, this estimate does not indicate how many of these Dutch patients might have been treated with Newcastle Disease Virus. Notably, this healthcare insurer indicated not to cover the costs of treatments by the MCC or Dr Gorter.

In August 2010 two videos on the MCC website presented testimonials of two Dutch cancer patients whom had received Newcastle Disease Virus:

- Mr CvH survives with a good quality of life more than 2.5 years in partial remission, his stage IV metastatic non-small cell lung carcinoma (NSCLC) through dendritic cell vaccinations in combination with hyperthermia and Newcastle Disease Virus.

- Mr WK survives now four years with lung metastatic primary liver cancer (Grade IV) (HCC = hepatocellular carcinoma liver) (caused by Hepatitis B) by combination treatment of Newcastle Disease Virus, dendritic cell therapy, hyperthermia and drips with natural immune stimulants.

Finally, the content of the MCC's website was changed several times in the period from May to August 2010. For example, in May 2010 it was possible to retrieve a document with information on treatment with Newcastle Diseases Virus, whereas in August 2010 this document was no longer available.

5. MAIN FINDINGS

This sections starts with an examination of the responses obtained from the supply side, followed by an examination of the responses from the demand side. This section closes with some observations and conclusions.

5.1 Findings from the supply side

In total, 69 different institutions and companies involved in 180 gene therapy clinical trials abroad were approached as potential suppliers of experimental gene therapy products. Taken into consideration that various institutions and most companies were involved in more than one gene therapy clinical trial, the overall response rate to queries for this study was about 60%. A large majority of these institutions and companies (83%) had information about possible enrolment of patients from the Netherlands in clinical trials with experimental gene therapy products, which they had conducted.

National authorities for clinical trials and/or GMOs in Belgium, Germany, Ireland and United Kingdom indicated not to be able to deliver the requested information and regularly referred to another authority or organisation in their country that might be able to provide a response. By contrast, national authorities in Austria, Switzerland and France were able to provide a response. Institutions involved in gene therapy clinical trials in Spain did not respond. Overarching institutions in the US, like the National Heart, Lung and Blood Institute and the National Cancer Institute, indicated not being able to respond.

Companies or organisations, such as Généthon, MolMed, Sanofi-Aventis (Schering-Plough), Transgene, and Telethon did not provide a response in contrast to Ark Therapeutics, Bayer Healthcare, Cardium Therapeutics, Ceregene, Oncolytic Biotech and Oxford Biomedica.

From all responses received from institutions and companies involved in gene therapy clinical trials, two cases of patients from the Netherlands who travelled abroad for treatment with experimental gene therapy products were found:

1. The University of Pennsylvania Medical Center in the US, which has been conducting Phase I clinical trials on adenoviral-mediated gene therapy for malignant pleural mesothelioma and other malignant pleural diseases since 1995, had one patient from the Netherlands in clinical trials in 2004, thereby noting that all trials have had close monitoring of viral shedding, demonstrating no virus in urine, sputum, faeces, etc., with no documentation of shedding of replication-incompentent adenovirus in any of the studies.

2. The Docrates Hospital in Finland treated one patient from the Netherlands with an oncolytic virus. Because of confidentiality, detailed information was neither provided on the nature of this oncolytic virus (species, wild type or a specific strain, replication competency, etc.), nor on the results of monitoring of viral shedding in this patient's urine, sputum, faeces, etc.

Further, on the website of the Medical Center Cologne in Germany two other cases of patients from the Netherlands treated with Newcastle Disease Virus (outside clinical trials) were

found. However, the total number of patients from the Netherlands treated with Newcastle Disease Virus could not be determined, as this clinic refused to respond to several queries by email and phone. The nature of the Newcastle Disease Virus used (wild type or a specific strain, replication competency, etc.), the way of its administration and the results of monitoring of viral shedding in these patients' urine, sputum, faeces, etc. could therefore neither be determined.

Since (cancer) patients from the Netherlands might have sought treatment with Gendicine or Oncorine, two gene therapy products that have been approved and registered in China, 80 upper-class hospitals with cancer treatment facilities in Beijing, Shanghai, Tianjin, Guangzhou and Shenzhen were approached with a request for information. However, despite the translation of the request for information into Chinese, none of these hospitals responded, except the Beijing Great Wall Hospital. SiBiono was also approached with a similar request, but no response was received. Sunway Biotech was not approached, as contact details could not be found on the Internet. Furthermore, the Dutch Embassy in Beijing indicated not being able to contact SiBiono or Sunway Biotech.

It is likely that only two hospitals (or hospital groups) in China are allowed to treat foreign patients, the Beijing Great Wall Hospital being one of them. On its website, three case studies were found on patients from the Netherlands, who had undergone gene therapy. Moreover, responses received from this hospital suggested that over the years only a few patients had come from the Netherlands for a treatment with Gendicine, while the information it provided on the results of monitoring of viral shedding in these patients was ambiguous.

5.2 Findings from the demand side

Responses obtained from organisations or associations of patients, healthcare practitioners and healthcare insurers in the Netherlands indicated that almost none of them had information about patients from the Netherlands who might have travelled abroad for treatment with gene therapy or oncolytic viruses.

One exception was the Dutch Ophthalmological Association (Nederlands Oogheelkundig Gezelschap), which had knowledge of two patients treated with lentiviral-based gene therapy against Leber's congenital amaurosis in Moorsfield Eye Hospital in London, UK. Though, it should be noted that lenti-viral based gene therapy is beyond the scope of this study, as Lentivirus is not on the list of viruses selected at the beginning of the second phase of this study.

The other exception was a major healthcare insurer, which estimated that two Dutch patients per year might travel to China for gene therapy, thereby noting that the costs thereof are not covered. This healthcare insurer further estimated that a few years ago about twelve Dutch patients per year went to the Medical Center Cologne, although not all of them would have necessarily been treated with Newcastle Disease Virus. However, the last years the number of Dutch patients visiting this clinic seemed to be declining.

5.3 Observations and conclusions

A main finding from the first phase of the study is that inspection services of the Netherlands government for healthcare (IGZ) and the environment (IMH) do not have information on patients from the Netherlands who might have travelled to other countries for treatment with experimental or registered gene therapy products.

Given the findings from different investigations of the supply and demand side in the second phase of the study, it is highly unlikely that over the last ten years more than a few patients from the Netherlands have actually sought treatment with experimental gene therapy products through participation in clinical trials abroad. Several responses from institutions and companies further suggested that it would be unlikely that foreign patients would have been enrolled clinical gene therapy trials, because that would have seriously complicated post-trial monitoring and follow-up care.

In fact, two cases have been found of patients from the Netherlands who have travelled abroad for an experimental gene therapy treatment. One to the US in 2004 for an adenoviral-mediated gene therapy within a clinical trial; in this case information was made available, indicating no viral shedding from the patient's urine, sputum, faeces, etc. And, more recently, one to Finland for a treatment with an oncolytic virus outside a clinical trial; in this case no further information was made available on the virus used and results of monitoring of viral shedding in this patient.

The study further identified the Medical Center Cologne in Germany as a clinic that had also been visited by cancer patients from the Netherlands for a treatment with Newcastle Disease Virus (outside a clinical trial). Their actual number could however not be determined. According to this clinic's website, at least two patients from the Netherlands have received treatments with Newcastle Disease Virus. In these two cases, no detailed information was found available on the virus used and results of monitoring of viral shedding in these patients were also not found available.

Moreover, it is highly unlikely that over the last five years more than a few patients from the Netherlands have actually travelled to China for treatment with Gendicine or Oncorine, two gene therapy products that have been approved and registered by the Chinese authorities. Yet, in these few cases, it is not clear whether viral shedding from these patients might have posed a risk to relatives, friends, medical practitioners and other third persons after their return in the Netherlands.

Despite the very limited number of patients from the Netherlands, who have actually sought treatment with experimental or registered gene therapy products abroad, it should be noted that in several of these cases detailed information was provided neither on the nature of the virus used in the treatment, nor on the results of monitoring of viral shedding in the patient's urine, sputum, faeces, etc. In these cases it is therefore virtually impossible to determine whether viral shedding from these patients might have posed a risk to relatives, friends, medical practitioners and other third persons after their return in the Netherlands.

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