Comment of the Paul-Ehrlich–Institut (PEI)
on the Proposal to amend Annex I to Directive 2001/83/EC regarding the definition of gene therapy and somatic cell therapy medicinal product
Public Consultation Paper No.2008-04-08

The definitions of gene therapy medicinal products (GTMP) and of somatic cell therapy medicinal products (SCT MP) are of eminent importance referring to the scope of the Regulation (EC) No 1394/2007. The proposals for updated definitions of gene therapy and somatic cell therapy medicinal products are suggested being slightly modified.

A. Proposal to optimize the proposed gene therapy medicinal product definition (GTMP)

Summary of issues posed by the proposed GTMP definition

The Paul-Ehrlich-Institut would like to bring to the attention of the EC that the proposed definition for gene therapy medicinal product (GTMP) poses major issues.

- A literally exact interpretation of the definition proposed by the EC (medicinal product is the active substance (DNA, vector, genetically modified cell, virus or microbe in, e.g., buffer or another formulation) leads to the conclusion that many GTMPs presently under investigation will be excluded (e.g., all viral vectors including those currently tested for vaccination/ immunotherapy, cardiovascular disease, hemophilia and other diseases, genetically modified cells including those tested to treat X-SCID and ADA-SCID, tumor vaccines) and another GTMP already proposed for market authorisation (Cerepro, a GTMP consisting of a replication-incompetent adenoviral delivery vector transferring the thymidine kinase gene of Herpes simplex virus (HSV-tk) into cancer cells in vivo). These products either contain added genes (in the genetically modified cells administered to patients) or they are all designed to <u>add</u> a genetic sequence to cells in vivo (viral vectors). In these cases, the added genes do not regulate, repair or replace a targeted genetic sequence.
- It is acknowleged, however, that there are MPs which add genes intended to regulate, repair or replace a targeted genetic sequence and we suggest including these MPs in the new GTMP definition. Future therapies may also involve the deletion and mutation of genetic sequences. After all, gene repair was the initial theoretical intention in gene therapy which will become a practicle possibility in the foreseeable future.
- The definition proposed by the EC may also include “conventional” live attenuated vaccines (encompassing an added gene or not) as well as live vector vaccines used to prevent infectious disease. These vaccines are sometimes termed “genetic vaccines”. The definition proposed by the EC also includes DNA/nucleic acid vaccines. The quality, safety and efficacy considerations used for GTMPs should also apply to these prophylactic vaccines against infectious diseases. If they were formally excluded from the definition, PEI proposes including such an obligation elsewhere in Annex I to Directive 2001/83/EC and to name these products “genetic vaccines”.

Listed below are the GTMP definition proposed by the EC followed by a modified definition proposed by the PEI which is aimed at solving the issues raised above. Although the definition may look complex, it has the advantage of describing rather exactly the products included in the novel GTMP definition. The GTMP definition suggested by the Paul-Ehrlich-Institut also takes into consideration current gene therapy developments in science, which may only in the midterm future lead to GTMP developments for clinical use. The Paul-Ehrlich-Institut prefers an exact, although complex definition over a general descriptive and less exact definition which would have to be explained by additional papers.

GTMP definition suggested by the Paul-Ehrlich-Institut (termed GTMP definition suggested by PEI in this paper)

Gene therapy medicinal product

means a medicinal product:

- the active substance of which contains or consists of a recombinant nucleic acid, where the recombinant nucleic acid is used in or administered to human beings with a view to regulating, repairing, replacing, adding, mutating or deleting a genetic sequence and/or where the recombinant nucleic acid is an added, mutated or deleted genetic sequence; and
- whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid it contains, or to the product of genetic expression of this nucleic acid or to cells harbouring a nucleic acid which has these properties. .

GTMP definition proposed by the EC in the Public Consultation Paper No. 2008-04-08 of 8 April 2008
(termed definition proposed by the EC in this paper)

Gene therapy medicinal product

means a medicinal product:

- that contains or consists of a nucleic acid sequence used in or administered to human beings, *in vivo* or *ex vivo*, with a view to regulating, repairing or replacing a targeted genetic sequence; and
- whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Reflections on the proposed GTMP definition

According to the perception of the Paul-Ehrlich-Institut the GTMP definition proposed by the EC includes the following products:
- any of the substances listed above, only if used “with a view to regulating, repairing or replacing a targeted genetic sequence” and “whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid (sequence) it contains, or to the product of genetic expression of this sequence”;
- siRNA, shRNA and other RNAs, if produced by biological methods or if contained in or produced by using biological starting material (e.g., PCR, cell-cell fusion, MIDGE DNA);
- plasmid DNA used in vivo (which is produced by biological methods);
- non-viral vectors containing plasmid DNA or biologically produced nucleic acids;
- linear single or double-stranded DNA and biologically produced oligonucleotides.

However, the proposed definition as of 08 April 2008 may exclude the following products:
- chemically synthesized RNA or DNA;
- RNA, oligonucleotides and plasmid DNA, if these substances or the products made in or by the cells from these substances are not intended to exert a therapeutic, prophylactic or diagnostic effect;
- RNA, oligonucleotides and plasmid DNA, if these substances are not administered “with a view to regulating, repairing or replacing a targeted genetic sequence”.

The Paul-Ehrlich-Institut would like to suggest changing the GTMP definition to reflect the following considerations:

1) The Paul-Ehrlich-Institut suggests including the following products in the GTMP definition:
- all replication-incompetent viral vectors (which all contain plasmid DNA or biological nucleic acids);

- all replication-competent vectors, which are recombinant micro-organisms and viruses carrying a therapeutic, in vivo diagnostic or preventive nucleic acid or carrying recombinant mutant or non-mutant wildtype genes;
- all cells genetically modified with a therapeutic, in vivo diagnostic or preventive nucleic acid including genetically modified cells where the genetic modification has led to a deletion, mutation or addition of a genetic sequence for a therapeutic, in vivo diagnostic or preventive purpose.
Therefore, added nucleic acids or nucleic acids intended to mutate or delete existing nucleic acids (knock-out mutations) should also be included in the GTMP definition.

All replication-incompetent vectors and all replicating (oncolytic) viruses can be included in the GTMP definition by stating that GTMPs are medicinal products
"- the active substance of which contains or consists of a recombinant nucleic acid, where the recombinant nucleic acid is used with a view to regulating, repairing, replacing, adding or deleting a genetic sequence…". This phrasing still excludes genetically modified cells because their recombinant nucleic acids will not be used with a view to regulating, repairing, replacing, adding or deleting a genetic sequence. This intended process is already completed within the genetically modified cells before they are administered as the active substance of a GTMP to patients/subjects.

In order to include in the GTMP definition cells which have been genetically modified to result in their nucleic acids being an added, mutated or deleted genetic sequence, this has to be stated in the definition. It is therefore suggested stating that GTMP means a medicinal product "… - the active substance of which contains or consists of a recombinant nucleic acid, where… the recombinant nucleic acid is an added, mutated or deleted genetic sequence;…".

We propose using the term "recombinant" nucleic acid because all GTMPs are prepared by recombinant DNA technology. Using this wording will exclude only non-recombinant oncolytic viruses. For non-recombinant oncolytic viruses, the GTMP considerations should still apply. It is suggested stating this elsewhere in Annex I to Directive 2001/83/EC.

If the EC intends to exclude cells genetically modified for other than preventive, in vivo diagnostic or therapeutic purposes in the final version of the new GTMP definition, the technical requirements for GTMP as listed in the GTMP-part of the revised Annex I to Directive 2001/83/EC should also be used for the genetically modified cells, even if these cells will be somatic cell therapy and/or tissue engineered products.

2) By using the term "in vivo or ex vivo" in the GTMP definition proposed by the EC, it was possibly intended to include nucleic acids used on cells in culture, i.e. ex vivo, in the GTMP definition and to allow applicants to obtain marketing authorisation for ex vivo used vectors. Usually only substances and preparations made from substances intended to be applied on or in the body are classified as medicinal products. We suggest deleting the phrase "in vivo or ex vivo" from the definition.

3) The term "nucleic acid sequence" relates only to a property of a nucleic acid, namely its sequence, but not to the substance "nucleic acid". We therefore propose using the term "nucleic acid". Nucleic acid is always more than one nucleotide, it can also be single stranded or double stranded. Oligonucleotides will also be nucleic acids.

4) The exclusion of preventive vaccines against infectious diseases from the GTMP definition will allow applying established principles and requirements for preventive vaccines. These are prophylactic nucleic acid/DNA vaccines, prophylactic non-viral vector vaccines, prophylactic live vector vaccines, replicating recombinant attenuated viruses or microbes used as prophylactic vaccines and recombinant hybrid viruses (the genome of which is a combination of the genome

of two viruses). Technically, the only possibility the Paul-Ehrlich-Institut has found to exclude such prophylactic vaccines is to state this exclusion accurately in the GTMP definition (see third hyphen of the GTMP definition suggested by PEI).

The Paul-Ehrlich-Institut would like to recommend ensuring that suitable gene therapy requirements in Annex I to Directive 2001/83/EC and in guidelines will also have to be met for these vaccines because some of the quality, safety, efficacy and environmental risk considerations of GTMP may apply to these vaccines, depending on a case-by-case evaluation.

5) By including after the second hyphen of the GTMP definition proposed by the EC, the wording "…- whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid it contains, or to the product of genetic expression of this nucleic acid;…" it was probably intended to exclude from the GTMP definition cells genetically modified with genes/nucleic acids which do not contribue to the therapeutic, in vivo diagnostic or prophalyctic purpose of the treatment of humans. Examples may be long established human cell lines containing neo genes which had been used during the establishment for the selection of cell clones, which could then be tested for a wished characteristic or property. Another example for such genetically modified cells may be cells harbouring recombinant nucleic acid mediating expression of cell surface markers, which can be used for in vitro selection, or "induced pluripotent stem cells". One may refer to these cells "cells genetically modified for manufacturing purposes".

However, recent science shows that human embryonic stem cell-like cells can be produced from human somatic cells by transferring nucleic acids encompassing three crucial genes using a retroviral vector. These cells (termed induced pluripotent stem cells (iPS cells)) could be starting material for human somatic cell therapay medicinal products. For this, the iPS cells would be differentiated to other human cells, e.g., blood stem cells, and then administered to patients. Some of the safety issues which these cells pose are currently believed to directly relate to the nucleic acid transfer. When these cells are administered to patients, however, the therapeutic effect will not relate to the transferred nucleic acids or products of their expression. The Paul-Ehrlich-Institut suggests applying to iPS cells and cells genetically modified for manufacturing purposes both, the principles and requirements for GTMPs and somatic cell therapy medicinal products..

The Paul-Ehrlich-Institut would like to draw attention to the fact that all genetically modified cells (harbouring a therapeutic, in vivo diagnostic or preventive nucleic acid) would possibly be excluded form the GTMP definition, if the phrase after the second hyphen would only be "…- whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid it contains, or to the product of genetic expression of this nucleic acid ". The reason for this is that the active substance of cell-containing GTMPs are the genetically modified cells, but neither the cells without the contained recombinant nucleic acid alone nor the recombinant nucleic acid not being part of the cells. In this sense, the effect of the cell-containing GTMPs therefore relates to the genetically modified cells in their entirety, not to the contained recombinant nucleic acid only nor to the cells without this nucleic acid.

B. Proposal to optimise the proposed definition of somatic cell therapy medicinal product (SCT MP)

Reflections on the proposed SCT MP definition

The proposed SCT MP definition excludes cells intended for immunotherapy use (see below) and should therefore be slightly reworded. The intention of the EC is welcomed to clarify that

“substantial manipulation, so that biological characteristics, physiological functions or structural properties” of cells in SCT MP should be equivalent to the meaning of “engineering” in the tissues engineered product (TEP) definition is welcomed by the Paul-Ehrlich-Institut.

Article 2(1) (c) of Regulation (EC) No. 1394/2007 says:
“Cells or tissues shall be considered ‘engineered’ if they fulfil at least one of the following conditions:
— the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,
— the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.”
Therefore, although it was probably intended to refer to the first hyphen only in Article 2(1), the chosen wording in the proposed definition refers to both hyphens, which is unfortunate.

Taken together, the proposed SCT MP definition as of 08 April 2008 (see below) therefore says that a somatic cell therapy medicinal product is:
“a medicinal product that
- contains or consists of engineered cells or tissues that have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved and
- is presented as having properties for, or is used in or administered to human beings with the view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.
The manipulations listed in Annex I (to Regulation (EC) No. 1394/2007), in particular, shall not be considered as substantial manipulations.”

This text would exclude SCT MP which are intended for immunotherapy because only “biological characteristics, physiological functions or structural properties *relevant for the intended regeneration, repair or replacement*” are named. SCT MPs for immunotherapy are not intended for regeneration, repair or replacement. To include under the term “SCT MPs” all cell-containing products with non-homologous use is in line with the current understanding that tissue engineered products are a subgroup of SCT MPs, although there are a few tissue engineered products which are not SCT products.

It is also recognised that cells genetically modified by therapeutic, in vivo diagnostic or preventive nucleic acid(s) will falls under the definition of SCT-MP and GTMP or TEP and GTMP. In this case and according to Article 2 No. 5 to Regulation (EC) No. 1397/2007, these genetically modified cells should be considered GTMPs.

SCT MP definition proposed by the Paul-Ehrlich-Institut
Somatic cell therapy medicinal product
means a medicinal product that:
- contains or consists of cells or tissues <u>that have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties have been altered,</u> and
- is presented as having properties for, or is used in or administered to human beings with the view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.
<u>The manipulations listed in Annex I to Regulation (EC) No. 1394/2007, in particular, shall not be considered as substantial manipulations.</u>”

SCT MP definition proposed by the EC in the Public Consultation Paper No. 2008-04-08 of 8 April 2008

Somatic cell therapy medicinal product
means a medicinal product that:
- contains or consists of engineered cells or tissues within the meaning of Article 2(1)(c) of Regulation 1394/2007/EC, and
- is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

Tissue engineered product definition according to Article 2 of Regulation (EC) No. 1394/2007

Tissue engineered product'
means a product that:
— contains or consists of engineered cells or tissues, and
— is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:
— the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations …