European Network for the Advancement of Clinical Gene Transfer & Therapy: CliniGene: www.clinigene.eu
jointly with
the "Regulatory Affairs and Ethics Committee" of ESGCT: www.esgct.org

European Society of Gene and Cell Therapy (ESGCT)

Comments on the consultation paper RE: Regulation (EC) No 1394/2007, Proposals to Amend Annex I to Directive 2001/83/EC as regards 'Advanced Therapy Medicinal Products'

I. General Comments

Given the complexity of the issues at stake and the suggestions for important changes that follow herein, maybe the Commission together with EMEA would be ready to **consider convening a "Clinigene/ ESGCT expert working sub-group at the GTWP" to examine and re-draft** important lines of the Advanced Therapy Medicinal Products documentation. Bringing together a group of people for a whole day to examine the detail of the document systematically might be benefitial to all parties at stake.

1. As this is an amendment to an annex of a Directive, the text should outline high level requirements only; that is general requirements. Detailed information should be described in 'guidance notes' or 'points to consider' documents rather than in this annex.
2. The number and section headings do not follow the original annex I which may lead to unnecessary confusion.
3. The number and section headings do not follow the excellent Note for Guidance on gene therapy medicinal products, i.e.: the "mother guideline" (CPMP/BWP/3088/99) which may lead to unnecessary confusion. In view of the general comment as of §1, it might be far more relevant for users and sponsors to refer to one master guideline as far as the structure and hierarchy of the points to consider in the application file/dossier are concerned.
4. For ease of understanding, review and use, particular requirements for GTMP should conceptually be integrated into the relevant modules of the Annex I.
5. The issue of the definition of gene therapy needs to be carefully thought of and if possible reconsidered, in view of the proposed text

II. Comments on the Definition of gene therapy medicinal products

Indeed, this is a very big shift from the current definition. It also moves away further and further from what most people understand gene therapy to be.

For reference: quotation of old and new definitions

Old definition:

"For the purposes of this Annex, gene therapy medicinal product shall mean a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either in vivo or ex vivo, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression in vivo. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell."

New definition:

GT means a medicinal product:

1. 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

2. 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.

Scope

The "new" definition is much shorter than the old one and as such, it is not clear whether the proposal means that the current wording would be lost. If this is so, then much of the explanation about how to interpret the definition by giving examples of the diversity of gene therapy products is also lost.

The first paragraph in the new definition really needs rewording. The currently proposed EC-definition of GTMP does not encompass viral vectors, genetically modified cells or replicating oncolytic viruses. It only encompasses nucleic acids, i.e. plasmid DNA used in vivo. This should be changed.

The quotation of examples is believed to be benefitial, with:

(i) clear examples of GTMP: viral, plasmid and ex-vivo cellular carrying eg, therapeutic genes, cancer immunotherapeutics, non-therapeutic marker genes, prophylactic vaccine genes, ribozyme and antisense genes;

(ii) conceptually borderline, but in fact GTMP: oncolytic viruses, genome editing tools (eg meganucleases, ZFNs);

(iii) so far of uncertain status: synthetic oligo- or poly-nucleotides (of increasing size and complexity); siRNA-treated cells and siRNA itself could be gtmps: it is difficult to understand why cells modified with siRNA-genes fall under gene therapy but cells modified using siRNA itself would not be gene therapy; live attenuated (but gene modifed) virus vaccines could or could not be gtmps

The second paragraph should also be changed as definitions should include therapeutic uses of genes to somatic cells, without narrowing function (e.g. expression) or origin (e.g. synthetic).

In essence, anything - *the definition should perhaps be "nucleic acid or nucleic acid analogue"*- that can tamper in a DIRECTED or TARGETED fashion with the human genome should be gene therapy. This need to be directed or targeted excludes DNA chelating agents which are of course not gene therapy products.

Rationale

Now gone is the notion that the GT product is expressed in a human (or animal) cell. This means that the product may be administered and exert its action anywhere in the body, from blood to lumen etc.

Genetically modified micro-organisms (GMO) were previously considered as starting material.and wisely so. With the new definition, they are now brought into gene therapy. They were previously NOT because the expression of the gene sequence takes place in the GMO itself, not in the human cell (as previously required). Hence, This is a very big shift in paradigm. There are GMO-based products used in infectious diseases (travellers diarrhoea, Crohns disease) and even in food (like yoghurts) that would now become gene therapy products. Is this desirable ? Is this wise ?

With the new definition, the distinction is now drawn at the level of introduction of genetic material (and product produced by translation), rather than its expression in a human cell - which would then make many more products gene therapy products. The spectrum of risk from gene therapy products is increased from viral integration into human generic material, to expression of genetic sequences (producing a gene product which may be toxic), to now the introduction of GMOs.

With the spectrum of products so wide, why even make a distinction between gene and cell therapy?

Also significantly altered is the technical requirements regarding module 3 on quality

The legislation needs to be clear whether in fact we need a specific "gene therapy" definition or not: we maybe do not since there will always be exceptions.

III. Specific Comments

A. Section 2.3.2, No 1:

This section seeks to define starting materials. This level of detail may not be correct for an annex. Does starting material mean active pharmaceutical ingredient (API)?

B. Section 2.3.2, No 5 (b):

(b) For products containing a microorganism or a virus, data on the genetic modification, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided.

This falls under section 2.3 (module 3) which deals with quality but requests biodistribution (tropism) and toxicology data (pathogenicity). Is the information requested here too specific for example?

C. Section 2.3.2, No 5 (c):

> *(c) Information shall be provided on all the materials used for the manufacture of the drug substance, including the products necessary for the genetic modification of human/animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps.*

Does the word 'products' (…*including the products necessary…)* refer to starting materials? It is unclear what is meant here.

D. Section 2.3.3, No 6 (a), (iii):

> *(iii) The potential variability introduced through the starting material (e.g.variability of donor population such as age, characteristics of cells) shall be addressed insofar as manufacturing process, validation, characterisation, control, stability are concerned, both for the active substance and the finished product.*

What do the words 'active substance' (…*for the active substance and …)* refer to? It is unclear what is meant here.

E. Section 2.3.4, No 1:

> **1.** For advanced therapy medicinal product containing medical devices, bio-materials, scaffolds or matrices, a description of the physical characteristics and performance of the product and a description of the product design methods shall be provided. The interaction and compatibility between genes, cells and/or tissues and the structural components shall be described.

When refereeing to 'genes' (…between genes, cells*…)* does this mean gene products?

F. Section 2.4.2, No 1:

> (a) *In vitro* and *in vivo* pharmacodynamic "proof of concept"studies should be provided using appropriate models and relevant animal species designed to show that the nucleic acid sequence provides its intended function (appropriate target organ, or cells, level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.

The paragraph should be changed as follows:

In vitro and *in vivo* pharmacodynamic "proof of concept"studies should be provided using appropriate models and relevant animal species designed to show that the nucleic acid sequence provides its intended function (appropriate target organ, or cells, level of expression and functional activity) *unless justified. Where possible the duration of the*

nucleic acid sequence function should be provided. The proposed dosing regimen in the clinical studies shall be provided.

G. Section 2.4.2, No 2 (a):

(a) Biodistribution studies, shall include investigations on persistence, clearance and mobilisation. Biodistribution studies should especially address the risk of germ line transmission.

The first sentence should end with *'unless justified*' (after mobilisation).

In addition, biodistribution studies do not usually involve analysis of mobilisation. Indeed it is hard to imagine how mobilisation studies can be carried out. For example for vectors such as those based on retroviruses. If the gene therapy used is a murine leukaemia virus (MLV)-based vector, infecting a rat or mouse with wild type (infectious) MLV will not inform on the safety of its use in humans who are unlikely to be infected with MLV. If another retrovirus were to be used, such as HIV-1, then infecting a rat or a mouse with this will also not lead to a productive infection and will therefore not be informative.
This paragraph requires that 'the risk of germ line transmission' should be especially addressed. It is unclear what this means as normally biodistribution studies do include the analysis of gonads, where appropriate. Is this guidance requesting additional studies on gonad administration? This would not be appropriate, as in most cases biodistribution studies are configured to follow the planned clinical route of administration.

H. Section 2.4.2, No 3 (c):

…. For those cases where single dosing may result in prolonged functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered…..

The reason for this point is unclear. If the nucleic acid has prolonged functionality then it does not need to be repeatedly dosed.

h

I. Section 2.4.2, No 3 (f):

(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, where appropriate according to relevant guidelines.

The requirement for the assessment of the effect of the GTMP on 'fertility and general reproductive function' is not always relevant as the patient population may be past reproductive age. To demand this assessment for all GTMP is too prescriptive. It may be more appropriate to request these studies if the GTMP is suspected of impacting on fertility.

J. Section 2.5.2, No 1:

1. *Human Pharmacokinetic (PK) Studies shall include the following aspects:*

- shedding studies to address the excretion of the gene therapy medicinal products;

- biodistribution studies, including distribution to gonads;
- pharmacokinetic studies of the medicinal product and the gene expression moieties (e.g. expressed proteins or genomic signatures).

The requirement for biodistribution studies including gonads is not feasible. The implication is that sampling of patients' muscle, liver, kidney, heart, brain and also the ovaries or testes Is required, which is rarely feasible or ethical. The biodistribution studies carried out in patients should be informed by the non-clinical biodistribution studies.

The paragraph should include the following changes as follows:

1. *Human Pharmacokinetic (PK) Studies shall include the following aspects:*
- shedding studies to address the excretion of the gene therapy medicinal products if the vector is applied in vivo;
- biodistribution studies, including distribution to gonads shall be informed by non-clinical biodistribution studies and considered only where appropriate and feasible*;*
- pharmacokinetic studies of the medicinal product and the gene expression moieties (e.g. expressed proteins or genomic signatures) unless justified.

K. Section 2.5.2, No 3:

The paragraph should include the following changes as follows (underlined):

3. Safety studies shall address aspects such as:
- neoplastic proliferation due to insertional mutagenicity where appropriate.

L. Section 2.5.3, No 3:

The paragraph should include the following changes as follows (underlined):

3. Safety studies shall address aspects, such as:
- distribution and engrafting following administration;
- ectopic engraftment;
- oncogenic transformation and cell/tissue lineage fidelity where appropriate.

M. Section **2.5.1**, No 8:

8. A strategy for long term safety and efficacy follow-up should be included in the Risk Management Plan.

The 'Risk Management Plan' is not referenced