Genetically modified cells: regulatory expectations for marketing authorization in Europe

Marcos Timón

AEMPS
The opinions presented here belong exclusively to the author and should not be considered as the official opinions of AEMPS, EMA or CAT.
13 April 2012
EMA/CAT/GTWP/671639/2008
Committee for Advanced Therapies (CAT)

**Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells**

<table>
<thead>
<tr>
<th>Draft Agreed by GTWP, CPWP, BWP</th>
<th>January-March 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation of CAT, SWP, EWP</td>
<td>April 2010</td>
</tr>
<tr>
<td>Draft Agreed by CAT</td>
<td>May 2010</td>
</tr>
<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>20 May 2010</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>30 November 2010</td>
</tr>
<tr>
<td>Agreed by CAT Gene Therapy Working Party</td>
<td>07 October 2011</td>
</tr>
<tr>
<td>Adoption by CAT</td>
<td>13 April 2012</td>
</tr>
<tr>
<td>Date for coming into effect</td>
<td>1 November 2012</td>
</tr>
</tbody>
</table>
Quality, non-clinical and clinical aspects of genetically-modified cells used as medicinal products irrespective of:

- the intention:
  - clinical indication
  - manufacturing
  - others (e.g. cells dedifferentiation)

- the origin:
  - Autologous
  - Allogeneic
  - Xenogeneic

- the type:
  - primary
  - established cell lines
Quality, non-clinical and clinical aspects of genetically-modified cells used as medicinal products

Not all will be classified as Gene Therapy medicinal products*

2.1. Gene therapy medicinal product

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

*Directive 120/2009
To reflect the experience gained with products at MAA, Scientific Advice and PRIME

To consider development of new tools for the genetic modification of cells (i.e. genome editing technologies)

To reflect the increase in clinical experience, especially with CAR-T cells and related products
Starting materials

Directive 120/2009

3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.
Starting materials

Directive 120/2009

3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.

- Directive only refers to GM-cells that are GTMP
- In the current guideline applicable to all GM-cells
- Extend to genome editing tools
Genome editing tools

GM-Cells guideline
Define genome editing starting materials:

- vector (viral or non-viral) carrying modifying enzyme coding sequence
- mRNA coding modifying enzyme
- modifying enzyme
- genetic sequence for modification (e.g. gRNA)
- ribonucleoprotein
- the modifying template (oligonucleotide, plasmid…)

and the components to produce them

When vectors, mRNA or proteins are used, the principles of good manufacturing practice shall apply from the bank system used to produce these materials onwards.
Quality:

Manufacturing:

✓ High-level guidance for genome editing protocols

✓ Align with recent new guidance (e.g. GMPs for ATMP)

✓ Remove request for RCV testing at release provided:
  ➢ testing performed at virus stock
  ➢ no RCVs formed during manufacturing

✓ Add a section on comparability
Quality:

Characterization and release controls:

- Testing requirements revised
- High-level guidance for testing genome-edited cells for clinical use (risk-based approach)
- Some specifics for CAR-T cells
Non-clinical:

- All sections revised to reflect experience and new developments
- Sub-sections with specific guidance for some product classes:
  - CAR-T cells and related products
  - iPS cells
  - Products derived from genome editing
Clinical:

- All sections revised to reflect experience and new developments
- Specific advice for CAR-T cells
- Genome editing products: not enough experience yet
What’s next?

✧ Draft likely to be approved in July 2018

✧ Guideline draft to be published immediately after

✧ Comments will be expected
Thank you!