MINISTERIO DE SANIDAD Y POLÍTICA SOCIAL

agencia española de medicamentos y productos sanitarios

Genetically modified cells: regulatory expectations for marketing authorization in Europe

Marcos Timón

AEMPS

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Draft Agreed by GTWP, CPWP, BWP	**January-March 2010**
Consultation of CAT, SWP, EWP	April 2010
Draft Agreed by CAT	May 2010
Adoption by CHMP for release for consultation	20 May 2010
End of consultation (deadline for comments)	30 November 2010
Agreed by CAT Gene Therapy Working Party	07 October 2011
Adoption by CAT	13 April 2012
Date for coming into effect	1 November 2012

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Scope of guideline

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

Modified bacteria are excluded

Scope of guideline

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;

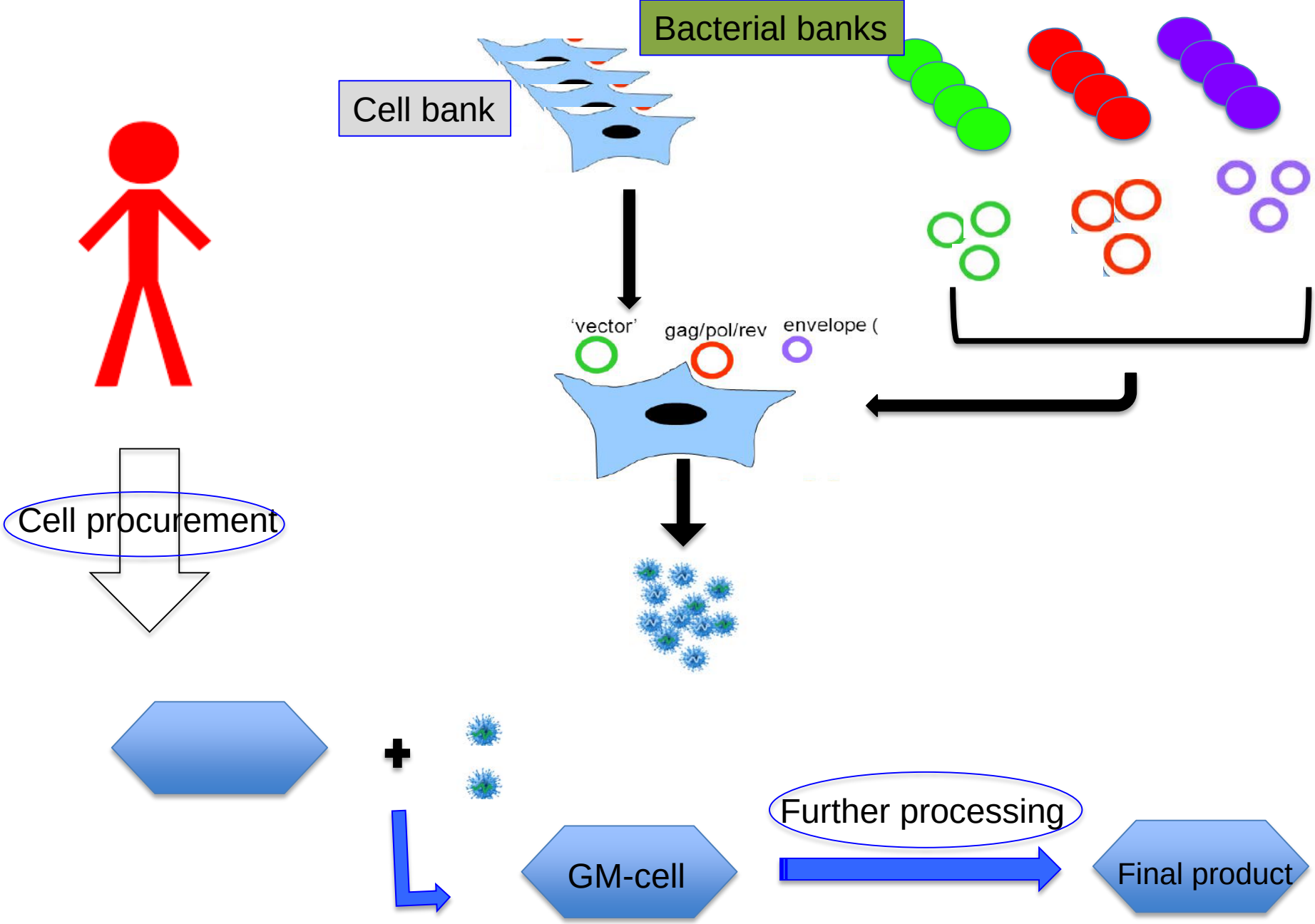
(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

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

*Directive 120/2009

Why updating?

- 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


Bacterial banks
Cell bank
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envelope (
Cell procurement
Further processing
GM-cell
Final product

GM-Cells guideline

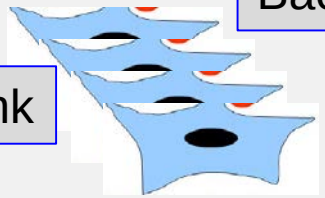
Starting materials

Directive 120/2009

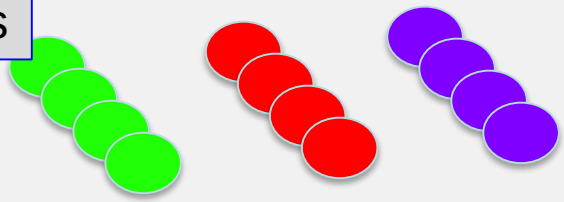
3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from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

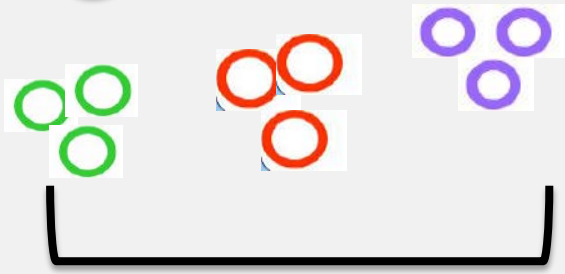
Cell procurement

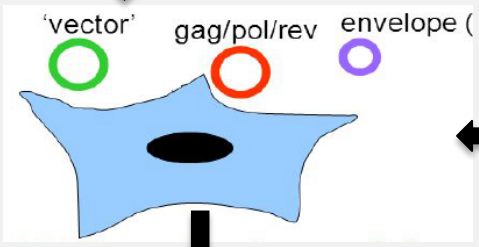
Cell bank

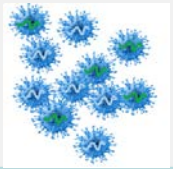


Bacterial banks



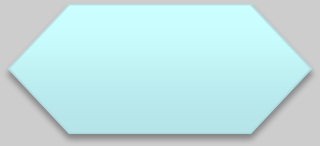


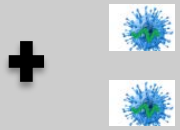




GMP principles

GMP





GM-cell

Further processing

Final product

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GM-Cells guideline

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.

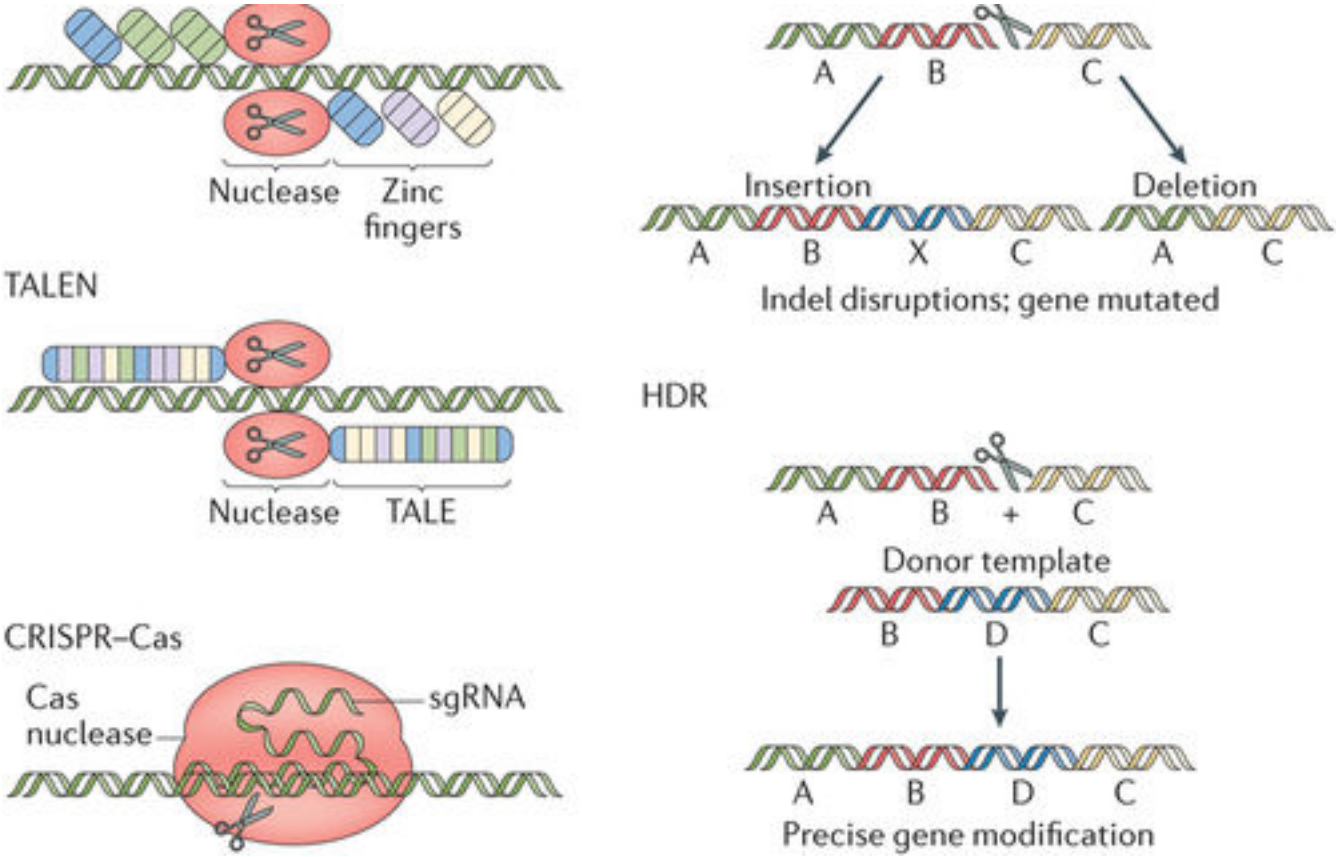
-Directive only refers to GM-cells that are GTMP

-In the current guideline applicable to all GM-cells

-Extend to genome editing tools

GM-Cells guideline

Genome editing tools



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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

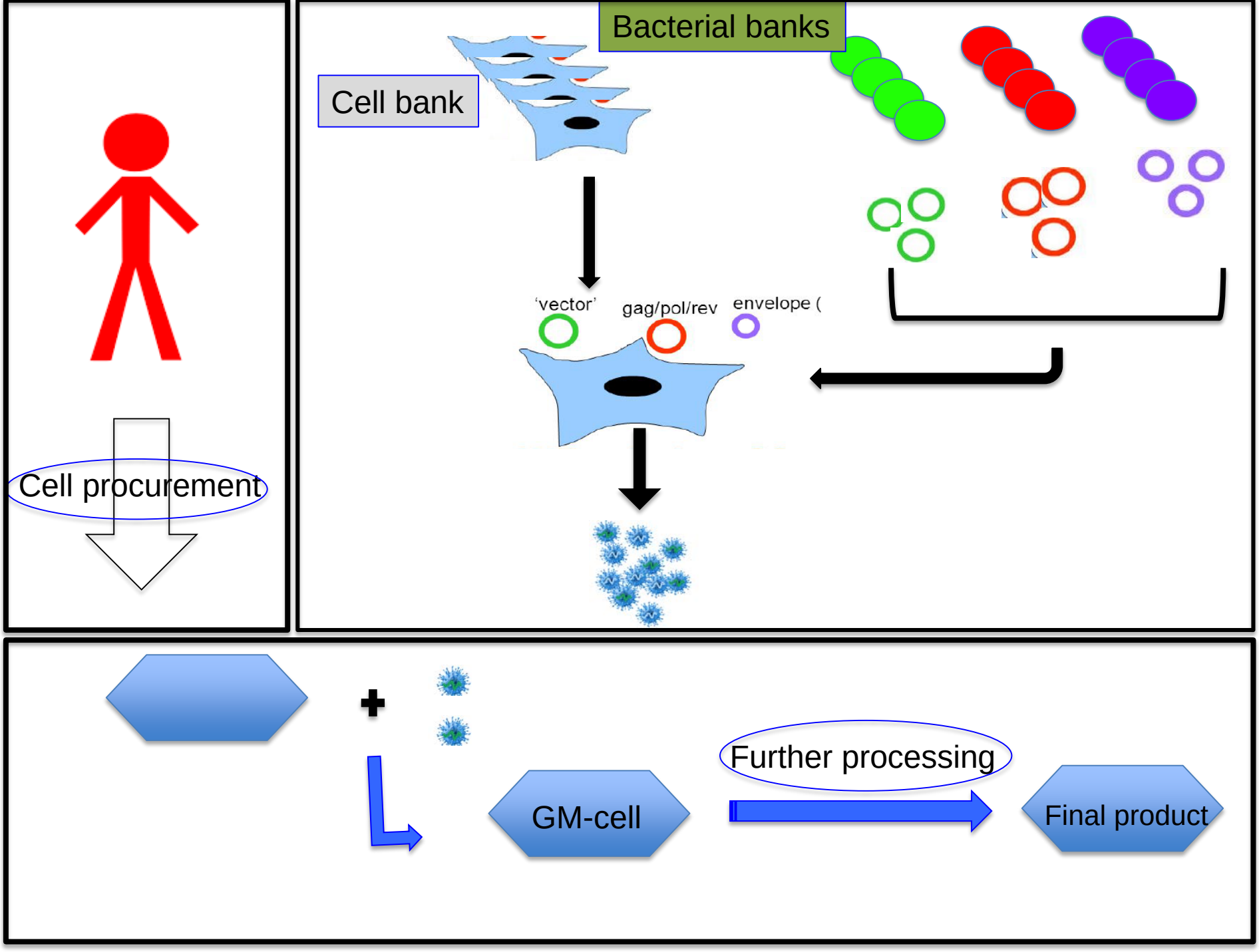
When vectors, mRNA or proteins are used, the principles of good manufacturing practice shall apply from the bank system used to produce these materials onwards .

What was updated?

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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What was updated?

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

What was updated?

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

What was updated?

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!