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SCIENCE MEDICINES HEALTH

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Committee for Advanced Therapies (CAT)

Concept paper on the revision of the Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

Agreed by BWP	12 July 2017
Adopted by CAT for release for consultation	14 July 2017
Adopted by CHMP for release for consultation	20 July 2017
Start of public consultation	24 July 2017
End of consultation (deadline for comments)	31 October 2017

The revised guideline referred to in this concept paper will replace guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008).

Comments should be provided using this template. The completed comments form should be sent to CATsecretariat@ema.europa.eu

Keywords	*Revision, genetically modified cells, quality, non-clinical, clinical, CAR-T cells, gene editing*

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1. Introduction

This Concept Paper proposes a revision of the Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008)[1] that came into effect in 2012. The guideline covers all cases of genetically modified cells intended for use in humans, independent of whether the genetic modification has been carried out for clinical indication (i.e. gene therapy medicinal products), for manufacturing purposes or any other reason. The genetically modified cells can be of human origin (autologous or allogeneic) or animal origin (xenogeneic cells), either primary or established cell lines. Genetically modified cells of bacterial origin are excluded from the scope of this guideline.

Work associated with the revision will include an analysis of existing information gathered for CAR-T cells and related products and propose revisions to the existing text where needed. The analysis will also consider recent developments on tools for the genetic modification of cells (namely genome editing technologies).

2. Problem statement

Since the current guideline[1] entered into force 5 years ago, scientific progress has been made in the field that needs to be reflected in the guideline. This affects primarily the availability of improved genome editing technologies which allow for simple approach to genetic modification of cells. The current guideline is focussed on genetic modifications by traditional methods, based on the use of vectors carrying recombinant nucleic acids. The newer technologies may use different starting materials and manufacturing processes. As these new tools potentially allow more precise gene modifications, different approaches to characterise and control modified cells are needed.

Apart from new tools, the use of genetically-modified cells has experienced an increase thanks to the clinical experience with CAR-T cells and related products in cancer immunotherapy. With many of these products under development and approaching marketing authorisation application[2,3], specific quality, non-clinical and clinical issues specific to CAR-T cells may need to be incorporated into the guideline.

3. Discussion (on the problem statement)

The current guideline[1] provides very general recommendations reflecting the state of the art at the time the guideline was prepared. Although genome-editing tools have been available for some time, their use was limited by several constraints including cost, complexity of use or difficulties to control specificity. This has recently changed thanks to the introduction of the CRISPR/Cas9 system together with improvements of some other approaches. The use of these technologies to genetically modify cells *ex vivo* for clinical applications has already started and is expected to increase rapidly. These tools use different starting materials and are able to achieve more specific genetic modifications than traditional vectors. These specific issues are not addressed in the current guideline, which mostly focuses on the use of vectors for the delivery of recombinant DNA. In addition, genome editing techniques raise new concerns such as off-target genomic modifications that need to be addressed and for which guidance is needed.

Furthermore, the dramatic increase in the use of genetically-modified cells for cancer immunotherapy, such as CAR-T cells, recombinant TCR T cells, etc. and genetically modified CD34+ cells for the treatment of haematological monogenic diseases, recommends a reassessment of the validity of the existing guidance text and the inclusion of specific guidance for the quality, non-clinical and clinical development of this type of products, where deemed appropriate in light of the existing experience.

Finally, since the publication of the guideline, a number of medicinal products containing genetically-modified cells have been approved[4,5] and many others have received scientific advice, providing experience to be incorporated into the guideline (e.g. target specificity and functionality, characterisation of integration efficiency and obtained cell populations, relevance of in vitro models (human cancer cell lines) for characterisation/ safety/ proof of principle, dosing and escape mechanisms/ safety during clinical use).

4. Recommendation

The CAT recommends a multidisciplinary revision of the current guideline[1] with the aim to:

-reflect significant development and experience gained since the publication of the current guideline

-reassess the validity of the existing guidance text in light of the existing experience

-provide, where needed, specific quality, non-clinical and clinical guidance for the development of CAR-T cells and related products,

-include considerations on the genome-editing tools when applied for the *ex vivo* genetic modification of cells.

5. Proposed timetable

It is anticipated that a draft revised guideline will be available by Q1 2018.

The concept paper is released for 3 months external consultation.

6. Resource requirements for preparation

The revision of the current guideline[1] will be led by the CAT in collaboration with the Biologics Working Party (BWP - responsible for quality aspects), Safety Working Party (SWP -consulted for non-clinical aspects), Oncology working party (ONCWP) and other relevant clinical experts.

A coordinating team will be appointed with representation from the above groups. Other relevant committees, working parties and external parties will be consulted as needed.

Drafting work will be conducted primarily by email and teleconferences; face-to-face drafting group meetings will be organized as needed.

7. Impact assessment (anticipated)

The revised guideline is expected to harmonise data requirements for applicants and ease assessment for regulators. It may contribute to streamline the development and ultimately marketing authorisation of medicinal products containing genetically-modified cells via the centralised procedure.

8. Interested parties

Bio-pharmaceutical industry and academia or other developers of gene and cell therapy medicinal products, academic networks and learned societies involved in the area.

9. References to literature, guidelines, etc.

1 Guideline on quality, non – clinical and clinical aspects of medicinal products containing genetically modified cells
(http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/05/WC500126836.pdf)

2 Mullard A. PRIME time at the EMA. Nat. Rev. Drug Discov. 2017; 16: 226-228

3 EMA PRIME microsite
(http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac05809f8439)

4 EPAR Strimvelis
(http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003854/human_med_001985.jsp&mid=WC0b01ac058001d124)

5 EPAR Zalmoxis
(http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002801/human_med_002016.jsp&mid=WC0b01ac058001d124)

For additional reference:

EMA Gene therapy guidelines:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000410.jsp&mid=WC0b01ac058002958d

EMA Cell therapy and tissue engineering guidelines:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000405.jsp&mid=WC0b01ac058002958a