Preclinical development of gene therapy drugs. Regulatory documents. Strategy. Experimental models. Potential risks when using gene therapy drugs. Toxicity

Problems in preclinical development of gene therapy drugs

- - Difficulty in accessing experimental models to evaluate effectiveness;
- - Lack of domestic regulatory documentation.

Foreign regulatory documents (FDA)

Guidance for Industry

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or e-mail address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2013

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24 June 2010
EMEA/CHMP/GTWP/587488/2007 Rev. 1
Committee for the Medicinal Products for Human Use (CHMP)

Reflection paper on quality, non-clinical and clinical issues related to the development of recombinant adeno-associated viral vectors

Draft Agreed by BWP/SWP/EWP/PhVWP/VWP	December 2008 - January 2009
Draft Agreed by GTWP	January 2009
Draft Agreed by CAT	February 2009
Adoption by CHMP for release for consultation	19 March 2009
End of consultation (deadline for comments)	30 September 2009
Agreed by GTWP/BWP	March-May 2010
Adoption by CAT	June 2010
Adoption by CHMP	24 June 2010

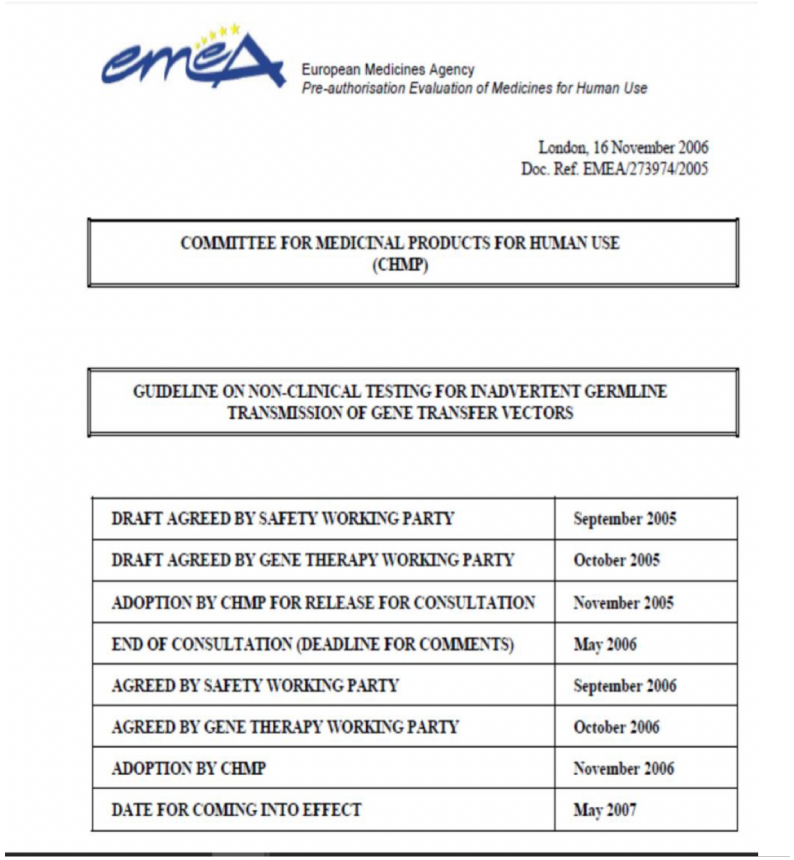
Keywords	*Adeno-associated virus, self complementary adeno-associated virus, recombinant adeno-associated virus, production systems, quality, non-clinical, clinical, follow-up, tissue tropism, germ-line transmission, environmental risk, immunogenicity, biodistribution, shedding, animal models, persistence, reactivation, advanced therapy medicinal product, gene therapy medicinal product*

Foreign regulatory documents

Аспекты программы доклинических исследований ГТЛП ***Aspects of GTMP non-clinical development programmes***	**Документ** ***Document***
Биораспределение *Biodistribution*	ICH guideline S12 on nonclinical biodistribution considerations for gene therapy products (EMA/CHMP/ICH/318372/2021) General principles to address virus and vector shedding. ICH considerations (EMEA/CHMP/ICH/449035/2009)
Перед первым применением у человека *Preclinical studies (before the first clinical use)*	Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006, 30 May 2008)
Репродуктивная токсичность *Reproductive toxicity*	Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005, 16 November 2006) General principles to address the risk of inadvertent germline integration of gene therapy vectors. ICH considerations (CHMP/ICH/469991/2006)
Риск для окружающей среды *Environmental safety*	Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products (EMEA/CHMP/GTWP/125491/2006, 30 May 2008) General principles to address virus and vector shedding. ICH considerations (EMEA/CHMP/ICH/449035/2009)
Модификация продукта разработки *Design modification of GTMPs*	Reflection paper on design modification of gene therapy medicinal products during development (CAT/GTWP/44236/2009, 14 December 2011)
Рекомбинантные аденоассоциированные вирусные векторы *Recombinant adeno-associated viral vectors*	Reflection paper on quality, non-clinical and clinical issues related to the development of recombinant adeno-associated viral vectors (EMEA/CHMP/GTWP/587488/2007 Rev. 1, 24 June 2010)
Онколитические вирусные векторы *Oncolytic viral vectors*	Oncolytic viruses (EMEA/CHMP/ICH/607698/2008)
Лентивирусные векторы *Lentiviral vectors*	Guideline on development and manufacture of lentiviral vectors (CHMP/BWP/2458/03, 26 May 2005)

Примечание. ГТЛП — генотерапевтический лекарственный препарат; ICH — Международный совет по гармонизации.
Note. GTMP, gene therapy medicinal product; ICH, International Council for Harmonisation.

Foreign regulatory documents



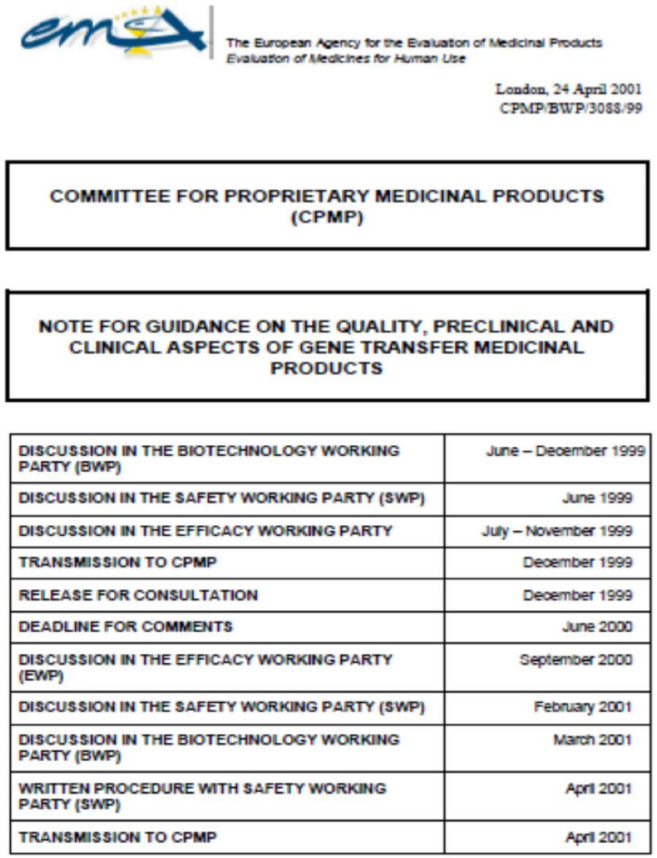
European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 16 November 2006
Doc. Ref. EMEA/273974/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

GUIDELINE ON NON-CLINICAL TESTING FOR INADVERTENT GERMLINE TRANSMISSION OF GENE TRANSFER VECTORS

DRAFT AGREED BY SAFETY WORKING PARTY	September 2005
DRAFT AGREED BY GENE THERAPY WORKING PARTY	October 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	November 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	May 2006
AGREED BY SAFETY WORKING PARTY	September 2006
AGREED BY GENE THERAPY WORKING PARTY	October 2006
ADOPTION BY CHMP	November 2006
DATE FOR COMING INTO EFFECT	May 2007



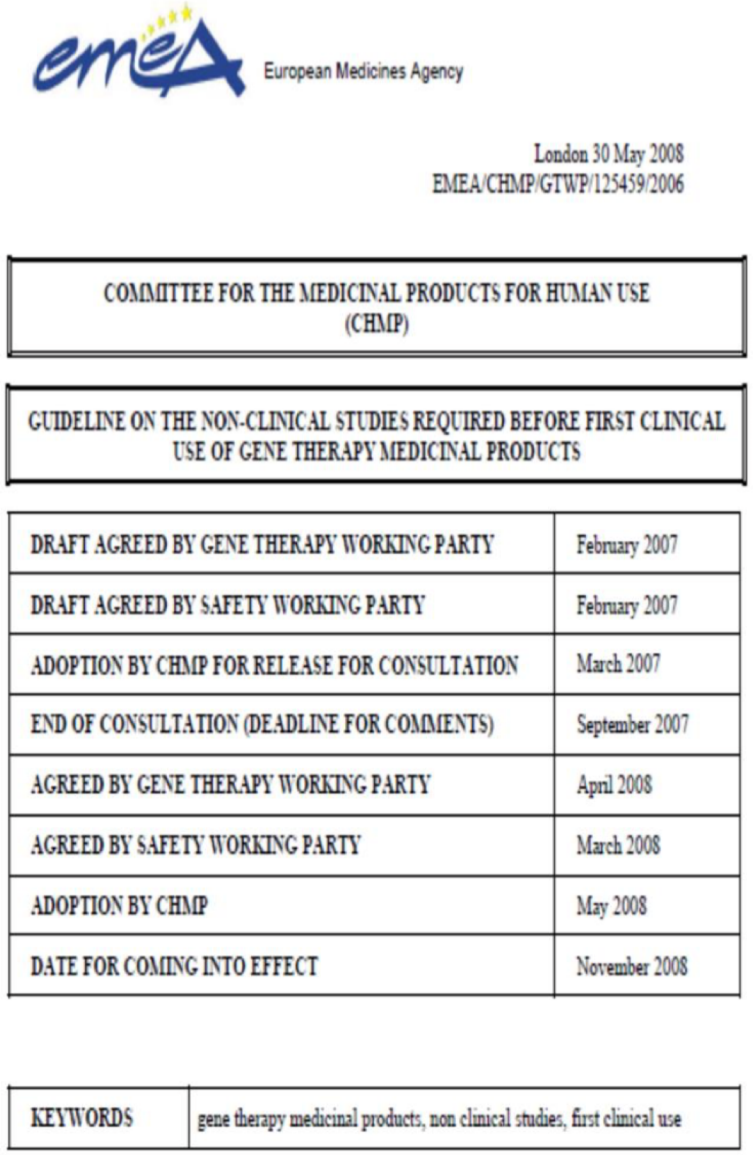
The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 24 April 2001
CPMP/BWP/3088/99

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)

NOTE FOR GUIDANCE ON THE QUALITY, PRECLINICAL AND CLINICAL ASPECTS OF GENE TRANSFER MEDICINAL PRODUCTS

DISCUSSION IN THE BIOTECHNOLOGY WORKING PARTY (BWP)	June – December 1999
DISCUSSION IN THE SAFETY WORKING PARTY (SWP)	June 1999
DISCUSSION IN THE EFFICACY WORKING PARTY	July – November 1999
TRANSMISSION TO CPMP	December 1999
RELEASE FOR CONSULTATION	December 1999
DEADLINE FOR COMMENTS	June 2000
DISCUSSION IN THE EFFICACY WORKING PARTY (EWP)	September 2000
DISCUSSION IN THE SAFETY WORKING PARTY (SWP)	February 2001
DISCUSSION IN THE BIOTECHNOLOGY WORKING PARTY (BWP)	March 2001
WRITTEN PROCEDURE WITH SAFETY WORKING PARTY (SWP)	April 2001
TRANSMISSION TO CPMP	April 2001



European Medicines Agency

London 30 May 2008
EMEA/CHMP/GTWP/125459/2006

COMMITTEE FOR THE MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

GUIDELINE ON THE NON-CLINICAL STUDIES REQUIRED BEFORE FIRST CLINICAL USE OF GENE THERAPY MEDICINAL PRODUCTS

DRAFT AGREED BY GENE THERAPY WORKING PARTY	February 2007
DRAFT AGREED BY SAFETY WORKING PARTY	February 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	March 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	September 2007
AGREED BY GENE THERAPY WORKING PARTY	April 2008
AGREED BY SAFETY WORKING PARTY	March 2008
ADOPTION BY CHMP	May 2008
DATE FOR COMING INTO EFFECT	November 2008

KEYWORDS	gene therapy medicinal products, non clinical studies, first clinical use

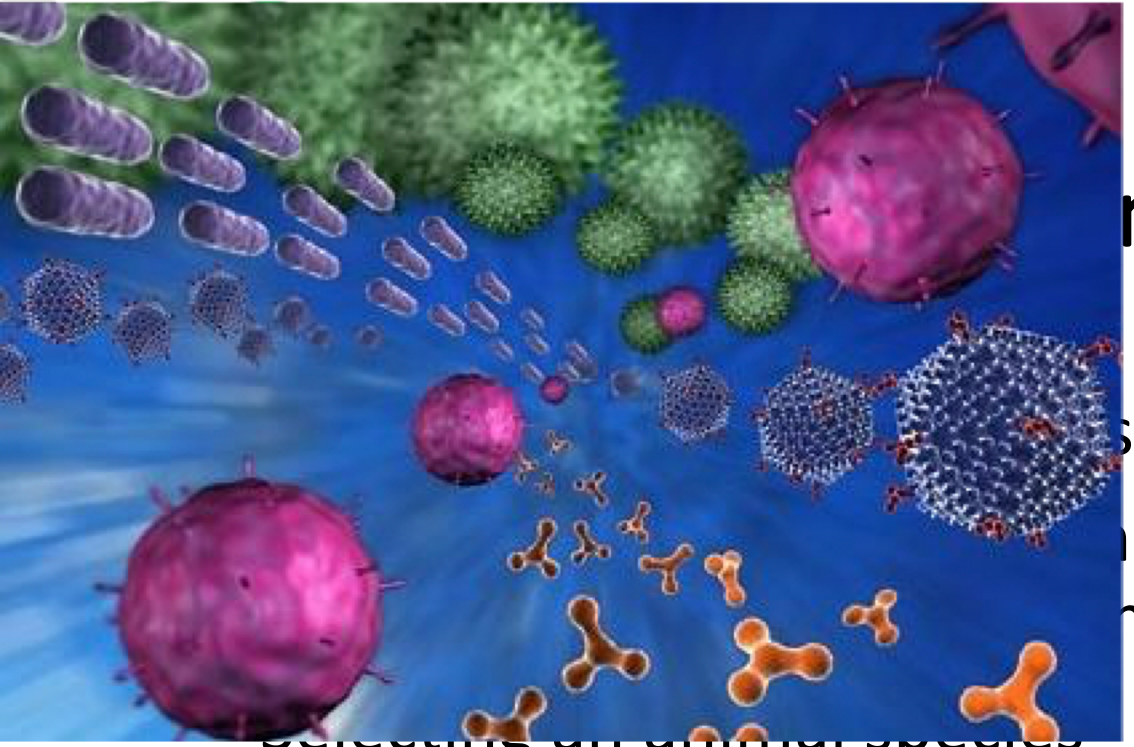
Preclinical Evaluation Strategy

- Demonstrated pharmacodynamic activity in an experimental disease model
- Biodistribution
- Recommendation of initial dose escalation and dose escalation schedule for use in a proposed clinical trial
- Identification of potential target organs of toxicity
- Identification of potential target organs of biological activity
- Determination of specific patient selection criteria

Experimental model

- In accordance with the provisions Reflection paper on quality, non-clinical and clinical issues related to the development of recombinant adeno-associated viral vectors
- Selecting an animal

species Species specificity of the vector The biodistribution of human virus serotypes may differ between animal species. Using serotypes of the virus to which the selected animal species is susceptible may be more appropriate than using the serotype that will be used in clinical trials.



mental model

sions

non-clinical and clinical issues related to
nant adeno-associated viral vectors

- Product specificity It is important to understand how immunogenic the transgene product will be for the selected animal species.
- It is possible to use the corresponding animal gene when conducting research.

Basic Research

- Pharmacodynamics
- Biodistribution
- Toxicity and safety
- General toxicity
- Reproductive
- Genotoxicity/Tumorigenicity

Pharmacokinetics study

- Biodistribution
- Data must be provided for all organs (both targeted and non-targeted)
- Data on the persistence of the transgene product must be provided
- The dose used should be consistent with that for clinical use

Potential risks of using gene therapy drugs

- Biodistribution of the vector/virus to non-target organs
- Level of viral replication and persistence in non-target organs and tissues o Inappropriate activation of the immune system
- Danger of insertional mutagenesis and/or oncogenicity
- Genetic modification of cells

Toxicity study

- The route and route of administration should be consistent with that for clinical use
- The doses used must provide a margin of safety for use in humans
- Relevant animal species must be used o Study duration is determined by ICH M3
- If the drug will be administered once in the clinic, it is sufficient to conduct only a single dose toxicity study

Other toxicities

- Integration Research o Tissue sensitivity testing
- Immunogenicity study o Immunotoxicity studies (for drugs that affect the immune system)
- Reproductive toxicity (only carried out if biodistribution studies show the presence of the vector in the gonads)
- Environmental risk assessment