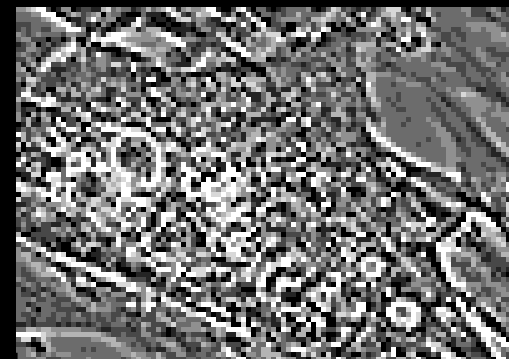
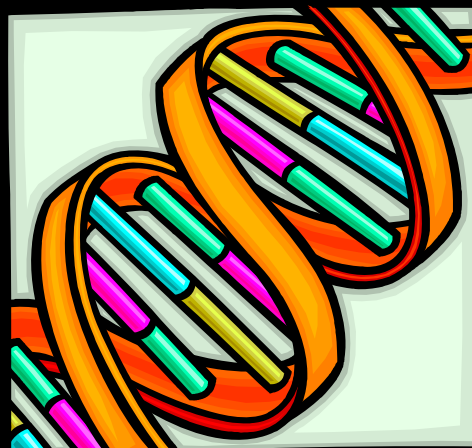
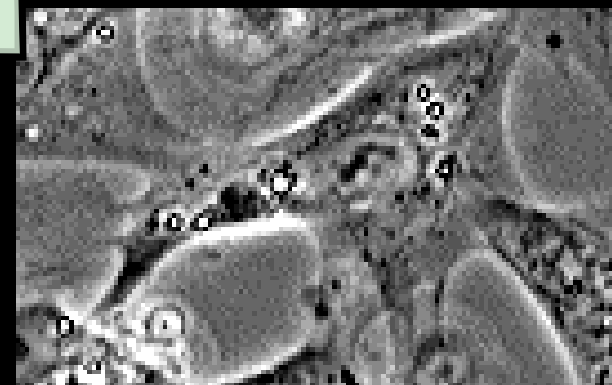


First Workshop on Advanced Therapy Medicinal Products (ATMP) - 3 April 2009

quality and manufacturing aspects of gtmps



cellsalive.com



cellsalive.com

Sol Ruiz

Spanish Meds Agency (AEMPS)



COMMISSION DIRECTIVE 2003/63/EC

of 25 June 2003

amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use

(Text with EEA relevance)

PART IV

ADVANCED THERAPY MEDICINAL PRODUCTS

Advanced therapy medicinal products are based on manufacturing processes focussed on various gene transfer-produced bio-molecules, and/or biologically advanced therapeutic modified cells as active substances or part of active substances

For those medicinal products the presentation of the Marketing Authorisation application dossier shall fulfil the format requirements as described in Part I of this Annex.

Modules 1 to 5 shall apply. For Genetically Modified Organisms deliberate release in the environment, attention shall be paid to the persistence of the Genetically Modified Organisms in the recipient and to the possible replication and/or modification of the Genetically Modified Organisms when released in the environment. The information concerning the environmental risk should appear in the Annex to Module 1.

1. GENE THERAPY MEDICINAL PRODUCTS (HUMAN AND XENOGENEIC)

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.

GENE THERAPY MEDICINAL PRODUCTS (HUMAN AND XENOGENEIC)

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1.2. Specific requirements regarding Module 3

Gene therapy medicinal products include:

- naked nucleic acid
- complex nucleic acid or non viral vectors
- viral vectors
- genetically modified cells



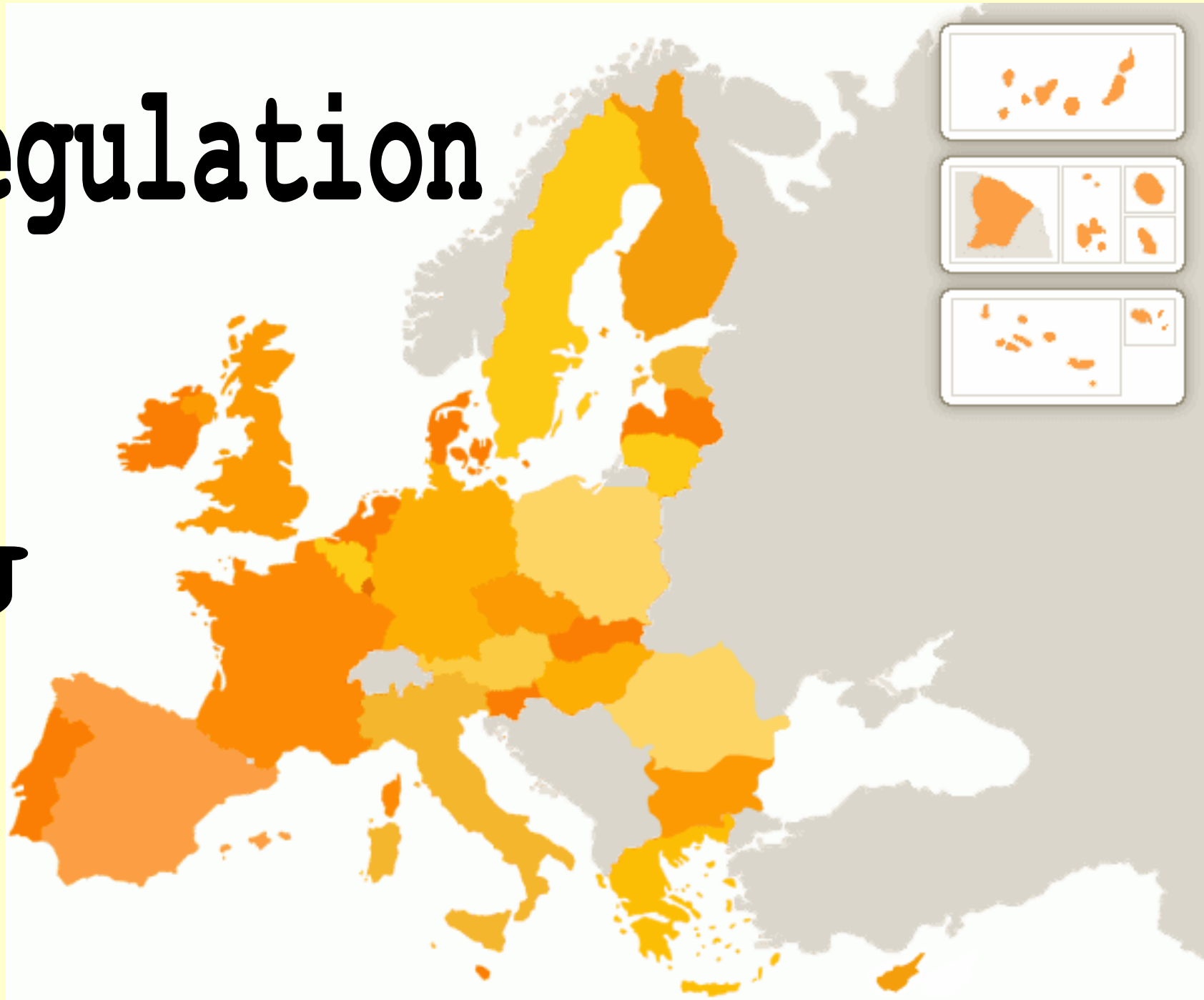
New proposal from the EC:

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.

GT regulation in the EU





- Directive on clinical trials
- EMEA guideline (annex on LV vectors)
- GTWP documents / ICH guidelines
- European Pharmacopoeia (*General Chapter*)
- Regulation on advanced therapies



- Directive on clinical trials
- EMEA guideline (annex on LV vectors)
- GTWP documents / ICH guidelines
- European Pharmacopoeia (gral chapter)
- Regulation on advanced therapies



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

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

DISCUSSION IN THE BWP	June-December 1999
DISCUSSION IN THE EWP, SWP...	
DATE FOR COMING INTO FORCE	October 2001



European Medicines Agency
Evaluation of Medicines for Human Use

November 2005

London, 26 May 2005
CHMP/BWP/2458/03

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON DEVELOPMENT AND MANUFACTURE OF
LENTIVIRAL VECTORS**

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

CPMP/BWP/3088/99

1. Introduction (*Scope*)
2. General considerations
3. Specific considerations
4. Considerations on the use of GMO
5. Preclinical evaluation
6. Clinical efficacy and safety
7. Glossary of terms

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

SCOPE

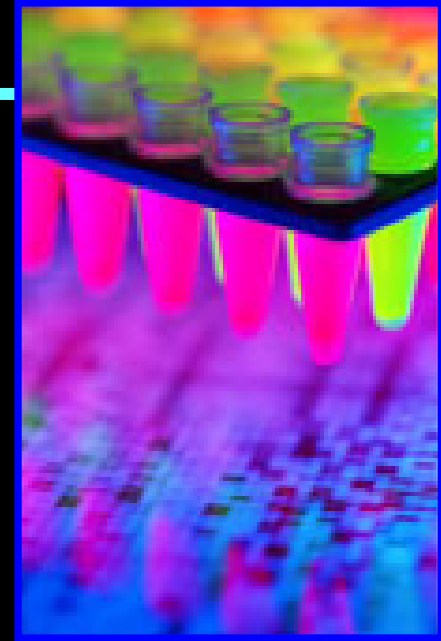
- ➔ addition and expression of a gene for therapeutic purposes
- ➔ inoculation of nucleic acids for the purpose of vaccination against foreign antigens
- ➔ transfer of nucleic acids with the aim of modifying the function or the expression of an endogenous gene

Chemically synthesized oligonucleotides not included

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

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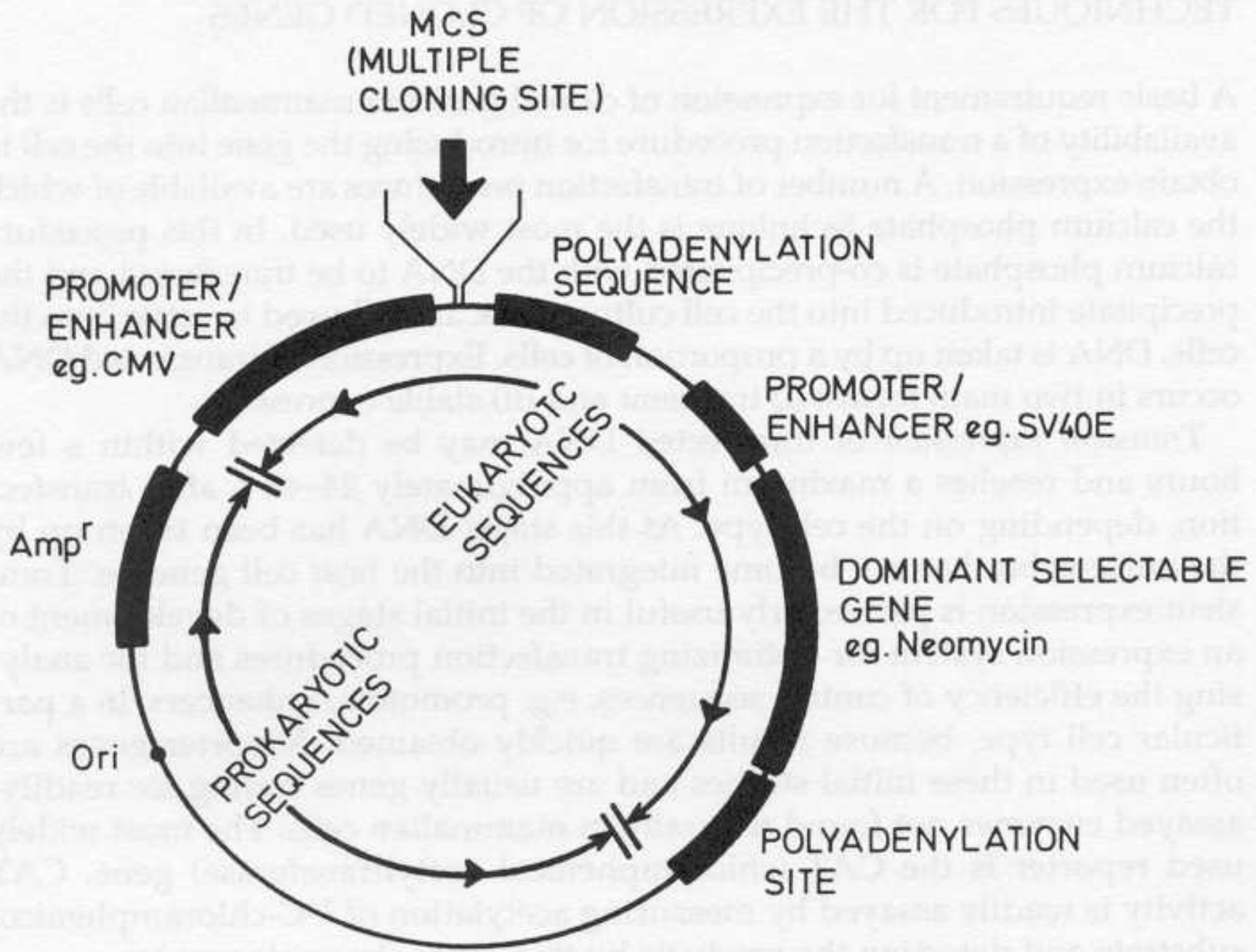
- Development genetics
- Production
- Purification
- Characterization
- Consistency of production
- Batch control analysis



development genetics

- Suitability of the vector and the delivery system
- Description and documentation of each element of the expression construct; scientific rationale based on their function and their inclusion in the expression vector
- Control and stability of gene expression

Also check ICH Q5B



development genetics

- Suitability of the vector and the delivery system
- Description and documentation of each element of the expression construct; scientific rationale based on their function and their inclusion in the expression vector
- Control and stability of gene expression
- Selection markers (atb resistance genes avoided when feasible)
- How the expression construct is incorporated into the vector

Also check ICH Q5B

production

- Vector
- Cells (bacteria, cell lines, primary cells)
- Cell Bank System (MCB/WCB)
- Viral Seed Lot system (MVS/WVS)
- Reagents (serum, growth factors, MoAb...)

TSE and viral safety (*guidelines, EurPh monographs*)

Preferably use reagents authorized as medicinal products if available

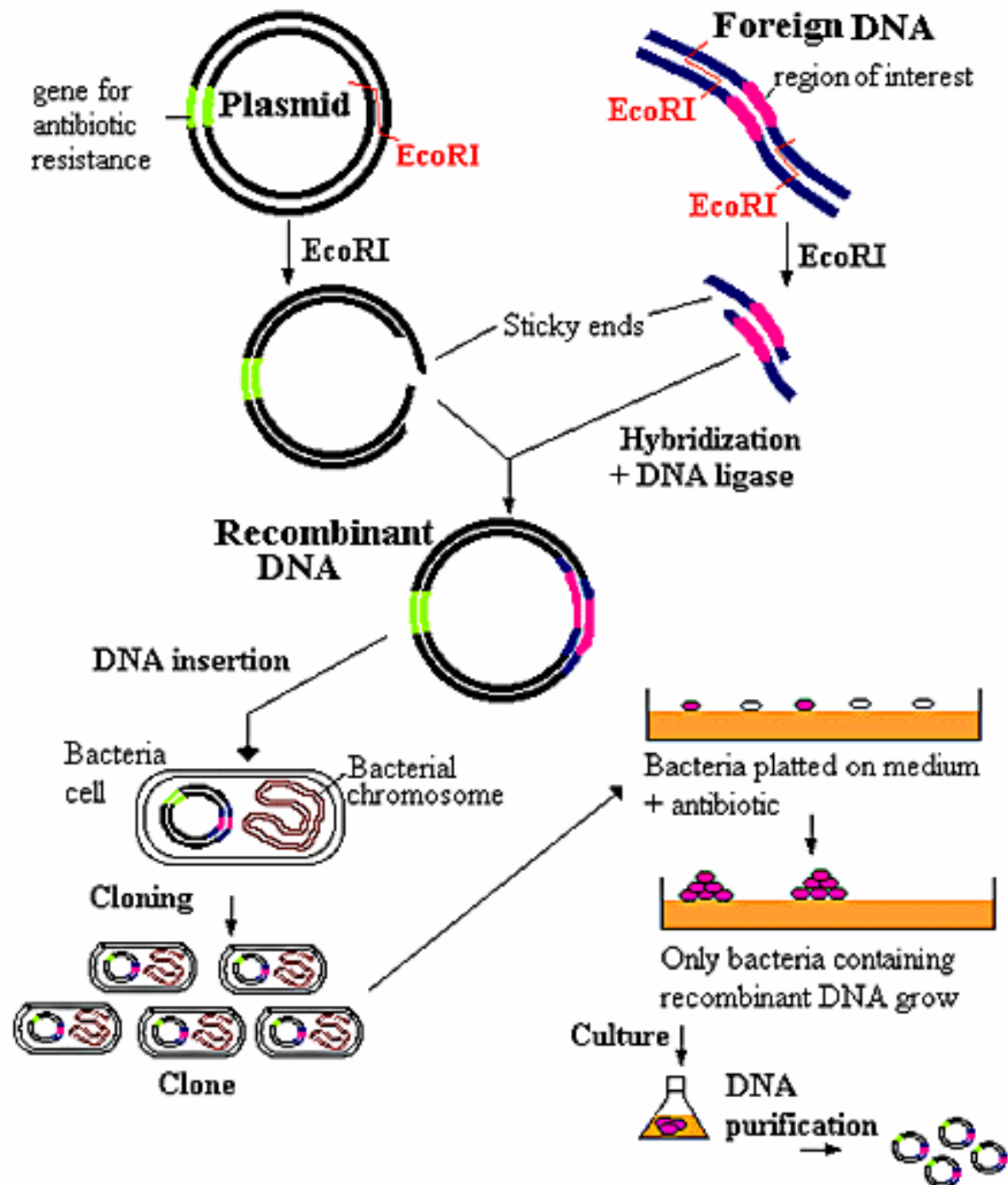
production

- MCB and WCB should be established where possible
- Well characterized virus seeds and/or cell banks
 - **identity, microbial and viral safety**
- Raw materials and reagents described and controlled according to relevant guidelines or EurPh requirements
- Detailed description and a flow chart; in-process controls (IPC)
- Viral vectors: full details of the packaging cell line and its microbiological safety
- Comparability studies

ICH Q5A-Q5B-Q5D-Q5E

purification

- Suitability of the purification process to remove impurities to an acceptable level
- Validated for the absence of extraneous viruses
- Control of materials of biological origin



IPC (in-process controls)

removal of reagents/
impurities (HCP, DNA...)

Cloning into a plasmid

characterization / consistency / safety

- Identity
- Purity
- Potency
- Stability
- Batch Release Specifications
- Safety requirements



characterization / consistency

- Characterization of the product and its components
- Suitable tests (biological, immunological, biochemical)
- Validated methods (for MAA)
- Justification of the specifications (limits for impurities)
- At least three consecutive batches (for MAA)

safety testing

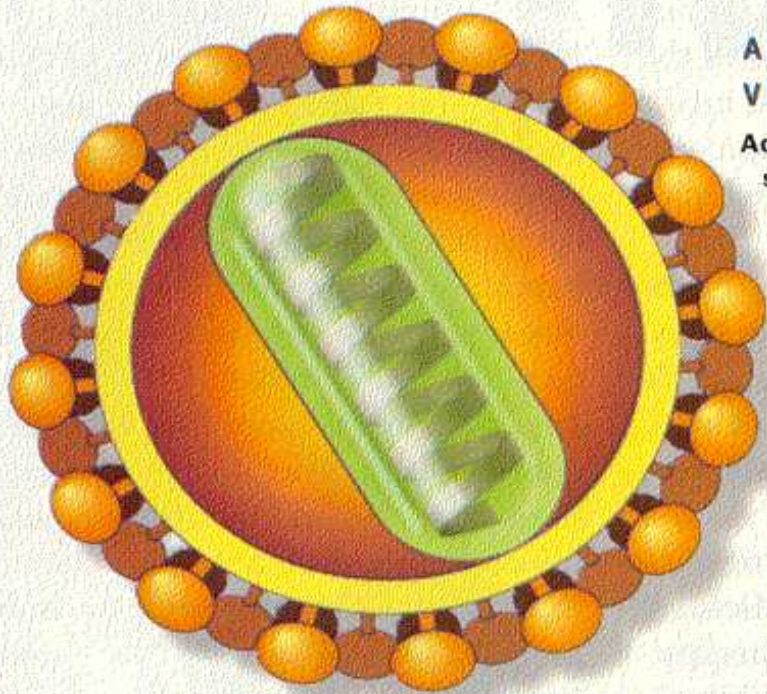
- Sterility
- Mycoplasma
- Pyrogens / endotoxins
- Freedom from adventitious agents
 - *in vitro* viral testing
 - *in vivo* viral testing
 - species-specific viruses
 - RCV

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

1. Introduction (*Scope*)
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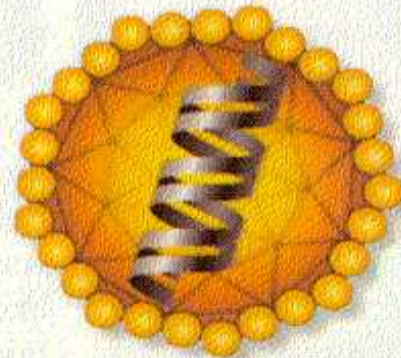
SPECIAL DELIVERY

Researchers are developing a variety of techniques for introducing healthy genes into patients' bodies. The method selected depends on factors such as the nature of the disease being treated and the size of the gene being transferred.



ADENO-ASSOCIATED VIRUS

Adeno-associated virus can insert itself into many types of cells without provoking an immune response, but can only carry small genes.

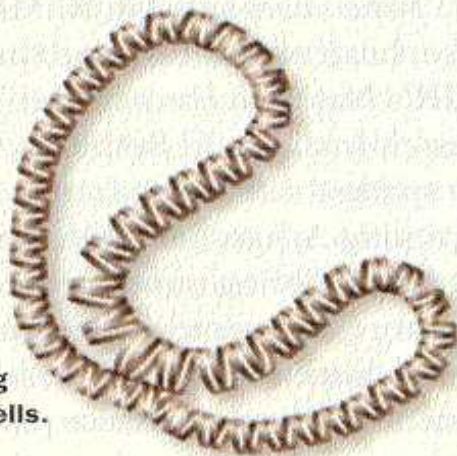


LENTIVIRUS

Lentivirus, a pared-down version of the HIV virus, can carry large genes—such as the one responsible for a blood clotting factor needed by hemophiliacs.

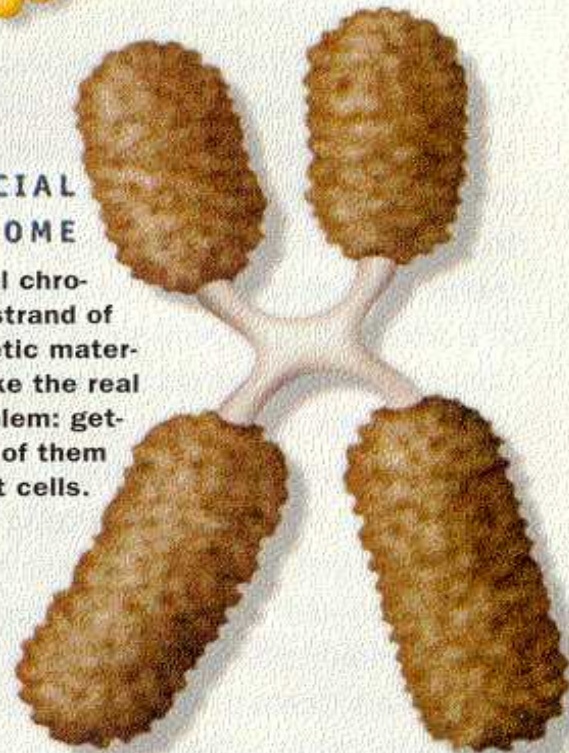
NAKED DNA

Naked DNA, a gene without any viral carrier, is injected directly into muscle and does not cause an immune response. But this method may be inefficient at getting genes into cells.



ARTIFICIAL CHROMOSOME

An artificial chromosome is a strand of synthetic genetic material that acts like the real thing. The problem: getting enough of them into the target cells.




 All documents

[Advanced Search](#) [Search Tips](#)

Scientific Guidelines for Human Medicinal Products

Background

Quality & Biologicals

[Quality \(Chemical & Herbal\)](#)
[Biologicals](#)

Non-Clinical

[Clinical Efficacy & Safety](#)

Multidisciplinary

Biologicals Guidelines

C = Concept Paper **D** = Draft Guideline **A** = Adopted Guideline **O** = Overview of Comments

Title	C	D	A	O	Reference Number	Publication Date	Effective Date	Other Remarks
Drug Substance								
Manufacture, Characterisation and Control of the Drug Substance								
Allergen products: Production and quality issues	◆				CHMP/BWP/304831/07	Release for consultation Sept 2007		Deadline for March 2008
Production and Quality Control of Monoclonal Antibodies and Related Substances	◆				CHMP/BWP/157653/07	Release for consultation May 2007		Deadline for Nov 2007
Potency testing of cell based immunotherapy medicinal products for the treatment of cancer <small>NEW</small>	◆		◆	◆	CHMP/BWP/271475/06	Dec 2007	May 2008	
Quality of biological active substances produced by stable transgene expression in higher	◆				CPMP/BWP/48316/06	Release for consultation Sept 2006		Deadline for Mar 2007



www.emea.europa.eu/htms/human/mes/advancedtherapies.htm

Medicines and Emerging Science

[Introduction](#)

[Innovation Task Force](#)

[Advanced therapies](#)

[Benefit-risk assessment](#)

[Biomarkers](#)

[Emerging technologies](#)

[How to get support from the EMEA?](#)

[Related information sources](#)

Advanced therapies

Below are guidance documents and other useful information resources relating to advanced therapies.

Further information relating to EU legislation on advanced therapies is available on the European Commission's [Pharmaceuticals website](#).

Gene therapy

- Gene Therapy Working Party (GTWP)
 - [Work Plan](#)
 - [Mandate](#)
 - [Reports](#)
- EMEA/CHMP guidance documents
 - [CHMP/GTWP/125491/06](#) Guideline on Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products (Deadline for comments August 2007)
 - [EMEA/273974/05](#) Guideline on Non-Clinical testing for Inadvertent Germline transmission of Gene transmission of Gene Transfer Vectors (Adopted by CHMP November 2006)
 - [Overview of comments](#) received on the above draft
 - [EMEA/CHMP/GTWP/203821/05](#) Concept Paper on the Development of a Guideline on the Non-Clinical Studies prior to Clinical use of Gene Therapy Medicinal Products (Released for Consultation November 2005)
 - [CHMP/BWP/2458/03](#) CHMP Guideline on Development and Manufacture of Lentiviral Vectors
 - [CPMP/BWP/3088/99](#) Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products
- ICH activities
 - [ICH website](#)
 - [EMEA/25059/02](#) ICH Communication Paper on First Workshop on Gene Therapy (held on 9 September 2002)

Contact Point

See also [How to get support from the EMEA?](#)

For further contact information see [Contact points](#)



European Medicines Agency

London, 25 September 2008
EMA/CHMP/GTWP/168855/2008

WORK PLAN
GENE THERAPY WORKING PARTY (GTWP)
2009

CHAIRPERSON: Klaus Cichutek

VICE-CHAIRPERSON: Maria Cristina Galli

STATUS: September 2008

- GM cells
- Patients' follow up
- Viral vectored vaccines
- DNA vaccines
- AAV vectors
- ICH topics



Guidelines >>



Regional Harmonization Initiative (RHI)
Profiles now online

Library of Presentations
and Training Materials

Contact the Quality IWG
with your comments and
questions on Q8, Q9, Q10



General
GCG related
MedDRA related
E14 related

text size: [s](#) [m](#) [l](#)

PUBLICATIONS

- Guidelines
- Step 2 Guidelines
- Questions & Answers
- Concept Papers & Business Plans
- Library
- Press Releases
- SC Reports & Other Documents
- New Topics
- C T D
- M2/ESTRI
- Find quickly what's NEW

CONFERENCES

- ICH Public Meetings
- ICH Previous Conferences

ABOUT ICH

- History and Future
- Structure of ICH
- Process for Harmonisation
- Glossary
- Frequently Asked Questions
- Contact Us
- Meetings Schedule

Global Cooperation Group

- Introduction
- RHI Profiles
- Training Activities
- Meetings & Reports
- Members

MedDRA

- Introduction
- Press Releases
- MedDRA Documents
- Management Board

GENE THERAPY

- Gene Therapy Discussion Group

Welcome to the official web site for ICH

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health. This Mission is embodied in the [Terms of Reference of ICH](#).

The ICH Secretariat can be contacted on admin@ich.org

*ICH Secretariat, c/o IFPMA, 15 ch. Louis-Dunant, P.O. Box 195, 1211 Geneva 20, Switzerland
Tel: +41 (22) 338 32 06, Telefax: +41 (22) 338 32 30*

**PUBLICATIONS**

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- Gene Therapy Discussion Group

GTDG Considerations Documents

GTDG ICH Considerations* are documents developed by the GTDG to report specific scientific considerations. These documents do not undergo the *formal ICH procedure* and therefore do not require the ICH Steering Committee to signoff. However, the documents still require discussion and endorsement by the ICH Steering Committee.

Please find as follows ICH Consideration Documents developed by the GTDG:

 [ICH Considerations on Oncolytic Viruses](#) dated November 13, 2008.
The Gene Therapy Discussion Group welcomes feedback on the ICH Considerations on Oncolytic Viruses. Please send your comments to the [Gene Therapy Discussion Group](#) by April 1, 2009.

 [ICH Considerations on General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors](#), 25 October 2006

 [Considerations from the Gene Therapy Discussion Group \(GTDG\)](#), Washington DC, June 2004

Considerations* : In order to avoid confusion with the M2 ESTRI Recommendations that follow the step-wise ICH process, the ICH Steering Committee requested that the outcome of GTDG discussions will now be called "Considerations", rather than "Recommendations".

Communication Papers

Following each GTDG meeting, the GTDG releases a Communication Paper to report on the outcome of its meeting.

Please find as follows Communication Papers from recent GTDG meetings:



25 October 2006

ICH Considerations

General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors

1. Introduction

Gene therapy vectors are designed to introduce genetic material into patients' cells for therapeutic, preventive or diagnostic purposes. Integration of delivered gene(s) into the genome of target cells represents the therapeutic goal in some clinical applications, for example when long-term efficacy/therapy is sought in genetic diseases. Also, vectors not generally considered capable of integration can do so at low frequencies. Integration of DNA might be desired or tolerated in target cells but should be minimised in non-target cells and is of particular concern for gonadal tissue where, although unlikely, there exists the potential for modifying the germline.

Integration events can result in insertional mutagenesis or genetic rearrangements that

ICH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH Considerations

Oncolytic Viruses November 13, 2008

1. Introduction

Oncolytic viruses (OV) were first observed in early clinical studies in patients with malignancies where tumour regressions were observed to coincide with viral infections or with live virus vaccinations. Since these early reports, studies using OV have progressed from anecdotal and controlled infections to specifically selecting or genetically modifying viruses for cancer treatment. OV are intended to propagate selectively in tumour tissue and spread, destroying the tissue without causing excessive damage to normal tissues.

For comments till April 1, 2009

5. GENE TRANSFER MEDICINAL PRODUCTS

The following **chapter** is published for information

This chapter contains a series of texts on gene transfer medicinal products (GTMP) for human use. The texts provide a framework of requirements applicable to production and control of these products. For a specific medicinal product, application of these requirements and the need for any supplementation is decided by the competent authority. The texts are designed to be applicable to approved products; the need for application of part or all of the texts to products used during the different phases of clinical trials is decided by the competent authority. The provisions of the chapter do not exclude the use of alternative production and control methods that are acceptable to the competent authority.

Further detailed recommendations on gene transfer medicinal products for human use are provided by the *Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99)* of the Committee for Medicinal Products for Human Use (including any subsequent revisions of this document).

GTMP for human use

5.1. Adenovirus vectors for human use

AAV

new texts

5.2. Poxvirus vectors for human use

RV

5.3. Plasmid vectors for human use

5.4. Bacterial cells used for the production of plasmid vectors for human use vectors for human use

ADENOVIRUS VECTORS FOR HUMAN USE

DEFINITION

Adenovirus vectors for human use are freeze-dried or liquid preparations of recombinant adenoviruses, genetically modified to transfer genetic material to human somatic cells *in vivo* or *ex vivo*.

PRODUCTION

VECTOR CONSTRUCTION

There are different approaches for the design and construction of an adenovirus vector. The purpose of clinical use determines which approach is optimal. A method is chosen that minimises the risk of generating replication-competent adenovirus vectors or that effectively eliminates ~~potential~~ helper viruses that might be used during production.

VECTOR PRODUCTION

The production method shall have been shown to yield a vector of consistent quality ~~in order to guarantee efficacy and safety in man~~. Unless otherwise justified and authorised, the vector in the final product shall have undergone no more passages from the master seed lot than were used to prepare the vector shown in clinical trials to be satisfactory with respect to safety and efficacy.

PURIFIED HARVEST

The purification process must be validated to remove impurities.

Vector concentration. Determination of the titre of infectious vector and the concentration of vector particles

Identification. Immunochemical methods (2.7.1) or NAT methods (2.6.21).

Genomic integrity. Verified by suitable methods (e.g. restriction analysis).

PURIFIED HARVEST

Residual impurities:

Host-cell protein

Host-cell DNA

Reagents

Antibiotics

Test unless the process has been validated to demonstrate suitable clearance

tests

Adv

Osmolality (2.2.35): within the limits approved for the particular preparation.

pH (2.2.3): within the limits approved for the particular preparation.

Extractable volume (2.9.17). It complies with the test.

Residual moisture (2.5.12): within the limits approved for the particular freeze-dried product.

Bovine serum albumin. Within the limits approved for the particular preparation determined by a suitable immunochemical method (2.7.1).

Replication competent adenovirus (RCA) concentration: within the limits approved by the competent authority.

tests

Adv

Vector aggregates. Vector aggregates are determined by suitable methods (e.g. light scattering).

Sterility (2.6.1). It complies with the test.

Bacterial endotoxins (2.6.14): not greater less than the limit approved for the particular preparation.

Thermal stability. Maintain samples of the vector final lot at a temperature and for a length of time that are adapted and authorised for the particular product. Determine the total infectious vector concentration after heating, as described below under Assay. Determine in parallel the vector concentration of a non-heated sample. The estimation of the difference between the total vector concentration without and after heating is within the limits approved for the particular product.

tests

ASSAY

Vector particle concentration. Physical titration is performed by a suitable technique (for example, liquid chromatography, absorbance measurement or NAT methods (2.6.21)). Use an appropriate vector reference standard to validate each assay. The vector particle concentration of the preparation to be examined is not less than the concentration stated on the label.

Infectious vector titre. Titrate the preparation to be examined by inoculation into cell cultures. Titrate an appropriate vector reference standard to validate each assay.

Ratio of vector particle concentration to infectious vector titre: within the limits approved for the particular product.

tests

ASSAY

Expression of the genetic insert product. The expression of the genetic insert product(s) is determined wherever possible, following inoculation of cell cultures with the product at a predetermined multiplicity of infection, by suitable immunochemical (2.7.1) or biochemical assays or by flow cytometry (2.7.24)

Biological activity. Unless otherwise justified and authorized, biological activity is determined by a suitable *in vitro* or *in vivo* test.



For internal consultation to Working parties - deadline: 9 January 2009
COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)
Draft 7

REFLECTION PAPER
ON QUALITY, PRE-CLINICAL AND CLINICAL ISSUES RELATING SPECIFICALLY TO
RECOMBINANT ADENO-ASSOCIATED VIRAL VECTORS

DRAFT AGREED BY GTWP	October 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	<day month year> ^[1]
END OF CONSULTATION (DEADLINE FOR COMMENTS)	<day month year> ^[2]
AGREED BY <WORKING PARTY> ^[3]	<month year>
ADOPTION BY CHMP	<day month year> ^[4]

^[1] Last day of relevant Committee meeting

^[2] Last day of the month concerned

^[3] If other WPs have been involved in discussions this needs to be specified

^[4] Last day of relevant Committee meeting

ICH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH Considerations

Oncolytic Viruses November 13, 2008

1. Introduction

Oncolytic viruses (OV) were first observed in early clinical studies in patients with malignancies where tumour regressions were observed to coincide with viral infections or with live virus vaccinations. Since these early reports, studies using OV have progressed from anecdotal and controlled infections to specifically selecting or genetically modifying viruses for cancer treatment. OV are intended to propagate selectively in tumour tissue and spread, destroying the tissue without causing excessive damage to normal tissues.

genetically modified cells

Target cell:

- Cell origin: autologous, allogeneic, xenogeneic
- Cell type: stem cells, cell line, lymphocytes...

Vector:

- Viral vectors (γ RV, LV, AdV, AAV) or non-viral vectors (plasmids)
- Permanent/transient/regulated expression

genetically modified cells

Production process

Manipulation under conditions to avoid cross-contamination

Process validated, IPC defined at key intermediate stages

Quality control:

Identity, viability, density, homogeneity, purity, biological activity, sterility, stability.

Integrity of expression, copy number, vector integration status, product identity and functional activity

RCV, residual vectors and other components where applicable

01/2007:2323

HUMAN HAEMATOPOIETIC STEM CELLS

Cellulae stirpes haematopoieticae humanae

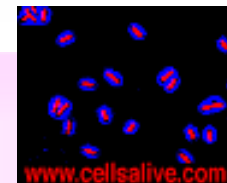
This monograph provides a standard for the preparation and control of human haematopoietic stem cells for use in therapy. It does not exclude the use of alternative preparation and control methods that are acceptable to the competent authority.

- **Numeration of CD34/CD45+ cells in haematopoietic products (2.7.23)**
- **Flow cytometry (2.7.24)**
- **Microbiological control of cellular products (2.6.27)**
- **Colony-forming cell assay for human haematopoietic progenitor cells (2.7.28)**
- **Nucleated cell count and viability (2.7.29)**

2.6.27. MICROBIOLOGICAL CONTROL OF CELLULAR PRODUCTS

This test has been shown to be preferable to the test for sterility (2.6.1) for certain cellular products, since it has better sensitivity, has a broader range, and is more rapid. It is applied instead of the test for sterility (2.6.1) where prescribed in a monograph. It may be carried out manually or using an automated system.

- **Growth promotion test**
- **Method validation**
- **Sample preparation , volume to test, analysis of the results**



case study
(live virus)

production

- Cell expansion from the MCB
- Cells infected with the MVSS. Incubation until full CPE is observed
- Cells harvested, sampled for testing, and stored frozen
- Freeze-thaw to release the virus
- Virus clarified by centrifugation and purified
- Buffer exchange and concentration
- Sterile filtration, sampling for testing and store frozen
- Thaw and pool
- Drug substance sterile filtered, sampled for testing and filled

development

Changes introduced during development:

- New MCB (Master Cell Bank)
- New MVS (Master Viral Seed)
- Scale-up of the production process
- Change in MOI (multiplicity of infection)
- Division of bulk harvest into sublots for purification
- Dialysis instead of TFF (tangential flow filtration)
- Addition of a freeze and hold step
- Addition of a filtration and hold step to DS
- Change in the DP filling facility

biotech product

Operating Parameters	Process Step	In-process Controls
<p>Load rate: 5 to 10 g/L resin Pool dilution factor: 4.5 to 5.5 fold Elution flow rate: 0.15 to 0.20 CV/min Pool hold temperature: 2.0- 8.0°C</p>	<p>Column: Cation exchange chromatography SP Sepharose HP resin, bed volume ~21.5 L</p>	<p>RP-HPLC purity, main peak: ≥ 86.8% CEX-HPLC purity, main peak: ≥ 81.8% SE-HPLC purity, main peak: ≥ 99.0% <i>E coli</i> protein: ≤ 2.5 ng/mg Bacterial endotoxin: < 0.24 EU/mL Aerobic bioburden: < 30 CFU/mL Step yield: 32.2% to 63.3% Pool volume: 40.9 to 77.4 L Position of start collect: 46.6 to 95.1 min Peak shape: Pass</p>

characterization

Identity:

SDS-PAGE and qualitative PCR

Content:

Total virus particles

Potency:

In vitro potency assay (cell line)

Impurities:

Process-related

Product-related

Potential contaminants

DS Specifications

Test	Method	Specification	Testing Facility
Physicochemical:			
pH	Ph Eur		
Content:			
Total virus particles/ml	In House method		
Identity:			
PCR	Contractors method		
Virus proteins (SDS-PAGE, Coomassie stain)	In House method		
Purity:			
Host cell protein (ELISA)	Contractors method		
Residual host cell DNA (PCR)	Contractors method		
Caesium chloride (Inductively coupled plasma mass spectrometry)	Contractors method		

Changes in the production of the DP:

- Facility 1 (Country A):

- Batches used in pre-clinical and early clinical studies
- Plastic cryovials

- Facility 2 (Country B):

- From batch X (pivotal toxicology) onwards
- Glass vials

Specifications of the DP

Test	Method	Specification	Testing Facility
General:			
Appearance	Ph Eur		
pH	Ph Eur		
Extractable volume	Ph Eur		
Subvisible particles	Ph Eur		
Content:			
Total virus particles/ml	In-House method		
Purity:			
Particle: infectivity ratio	In-House method		
Potency:			
Potency assay	In-House method		
Safety:			
Endotoxin	Ph Eur		
Sterility	Ph Eur		
Abnormal toxicity	Ph Eur		

Major problems during the evaluation:

Cell Banks

- Different cell banks used during development
- Insufficient characterisation of early used banks
- Lack of comparability studies between historical cell banks and final MCB
- Insufficient stability data for the final MCB

Viral Stocks

- Several viral stocks used during development
- The proposed commercial viral stock not used in clinical trials
- Insufficient characterisation of previous stocks
- Lack of comparability studies between historical stocks and final viral stock

Characterisation

- Tests proposed insufficient
- Analytical procedures not completely validated

Production process

- Processes and tests need full validation
- Proper comparability studies are needed
- Consistency of proposed production processes needs to be shown

Stability

- Additional data needed to support the proposed shelf-life

critical issues

QUALITY

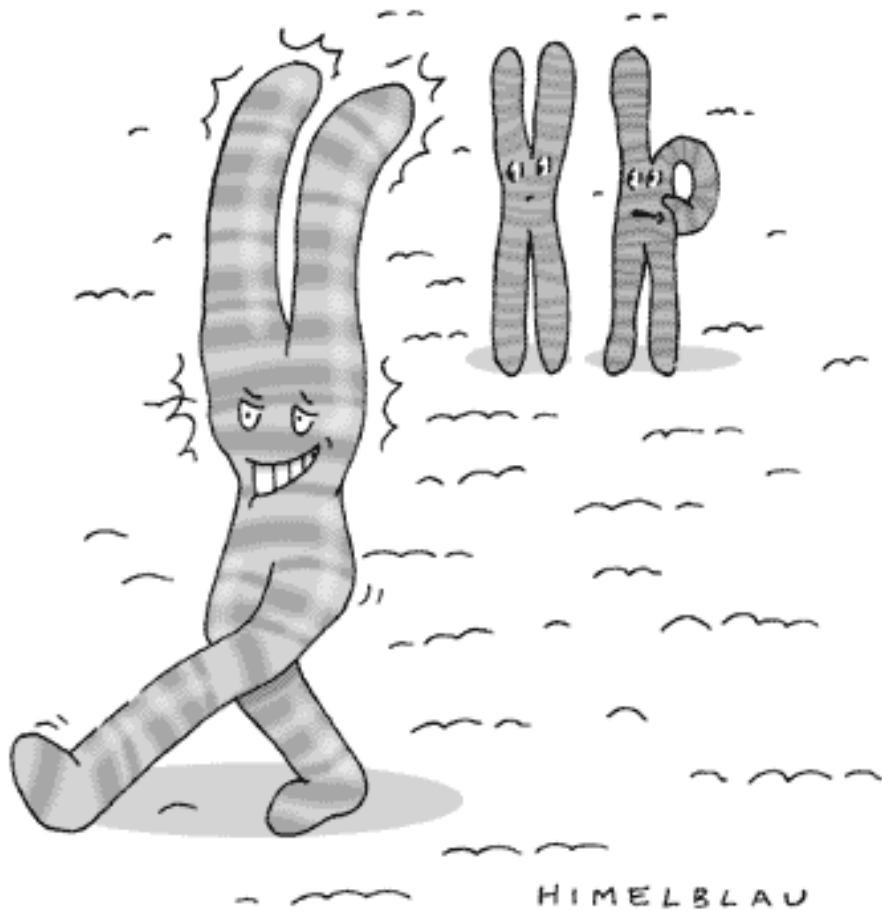
Viral/microbiological safety

Control of the manufacturing process / reagents

Identity, purity, potency and stability of the vector

Comparability

- Give the rationale for your approach
- Provide justification where data may be insufficient (RA)
- Request advice from early development



Sure he looks great... You would too
if you had designer genes.

thanks!

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