



atmp

in the

EU

role of the

BWP

Sol Ruiz - AEMPS

Biologicals



due to its complexity it cannot be fully characterized by analytical testing alone

quality determined by a combination of *physico-chemical and biological testing*, together with the *production process and its control*

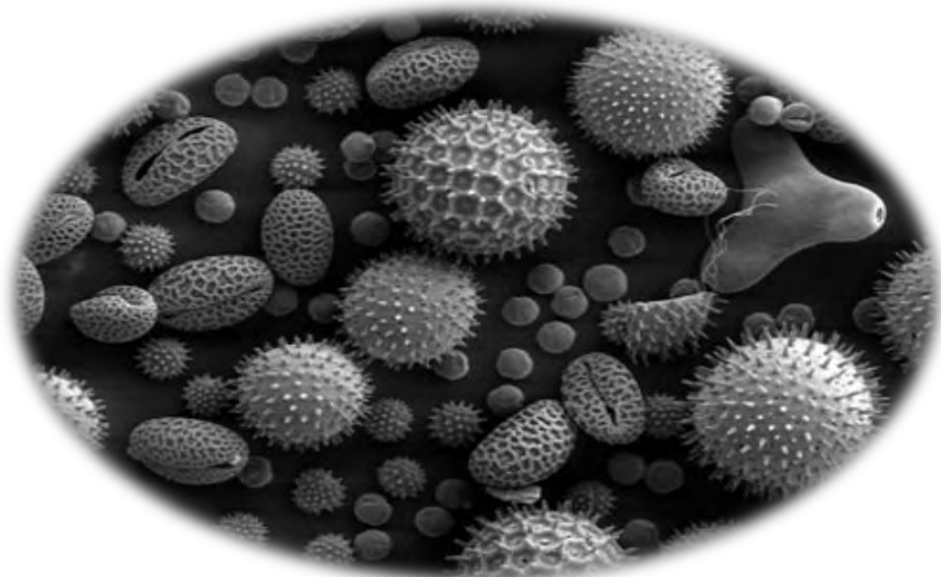
biological activity and immunogenicity are dependent upon all its *structural features*

vaccines

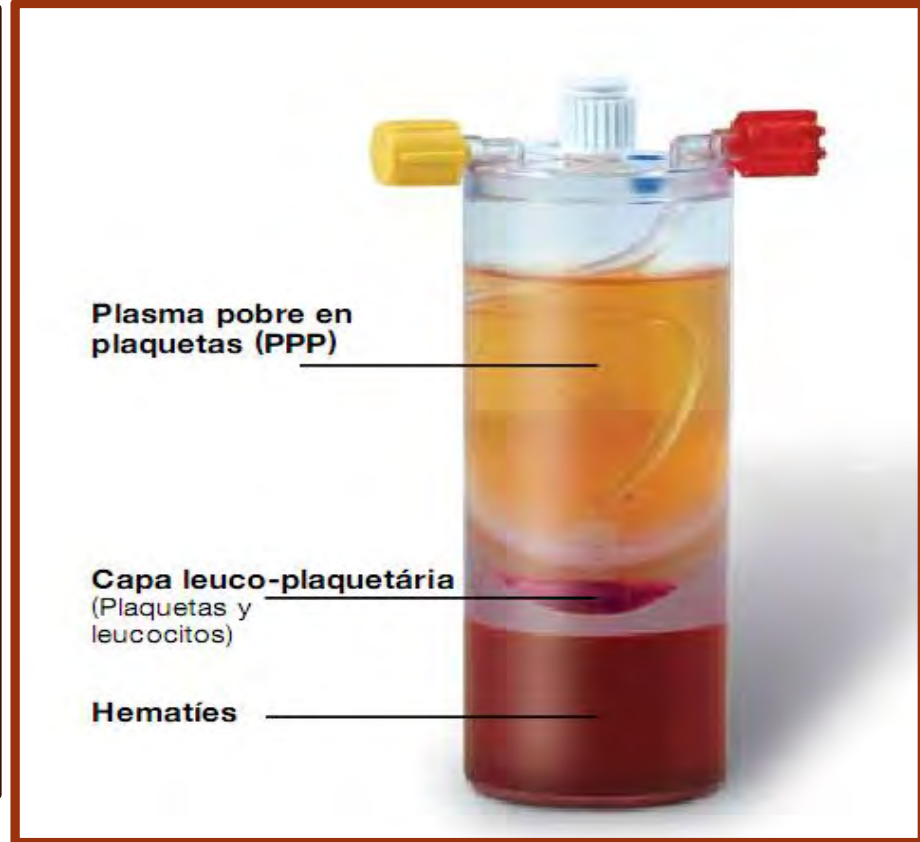
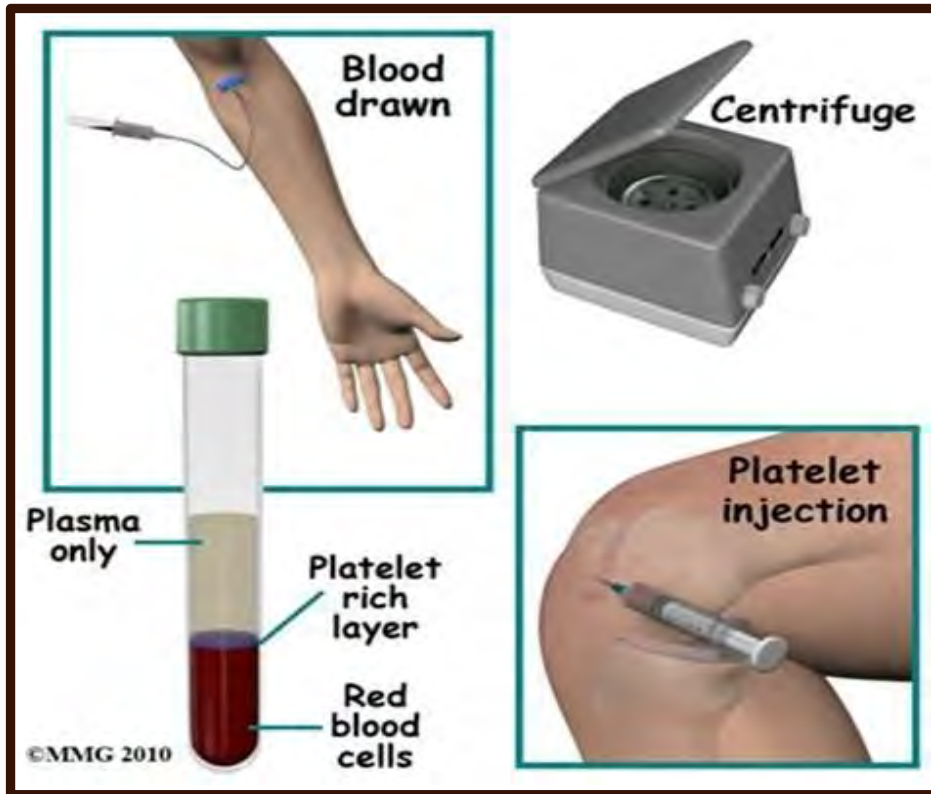


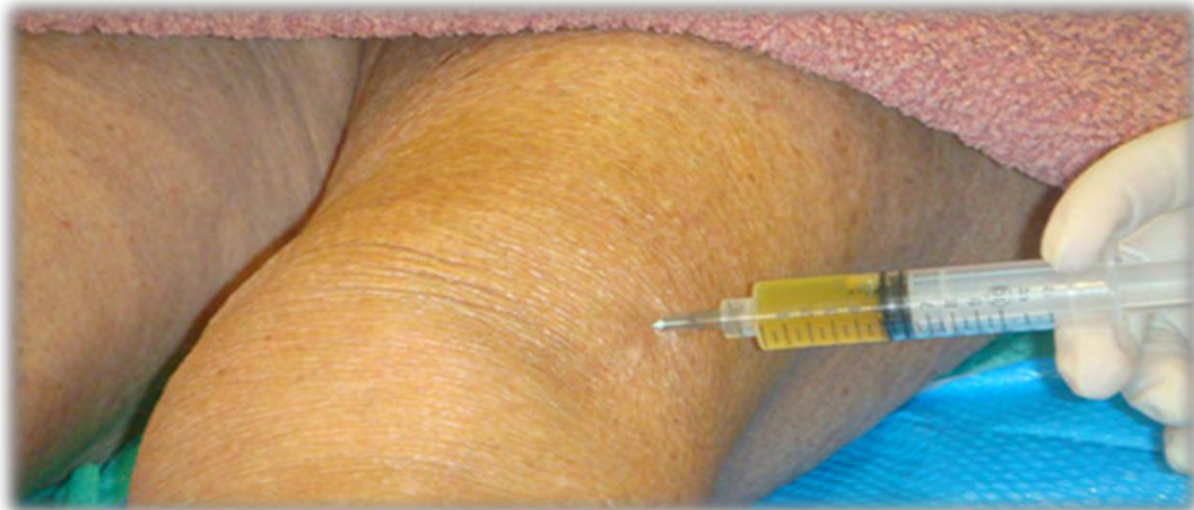
Plasma derived





autologous plasma (PRP)





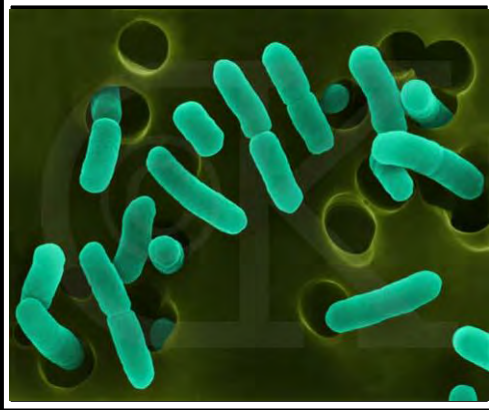
vaccines



Plasma derived



Biotechnological

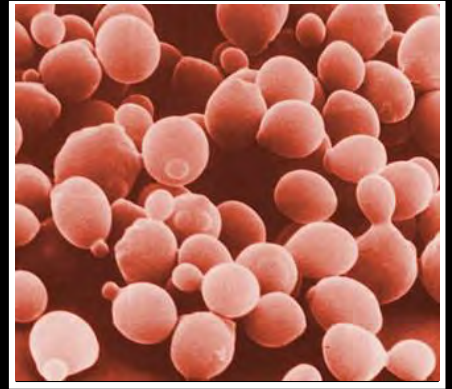


Bacteria

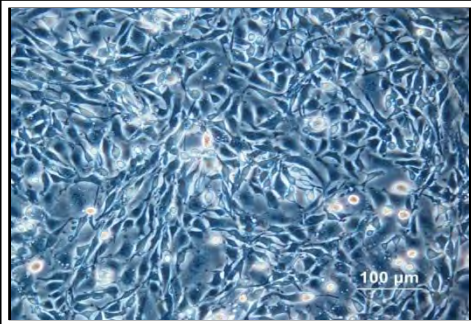
E. coli

Yeast

Saccharomyces



host

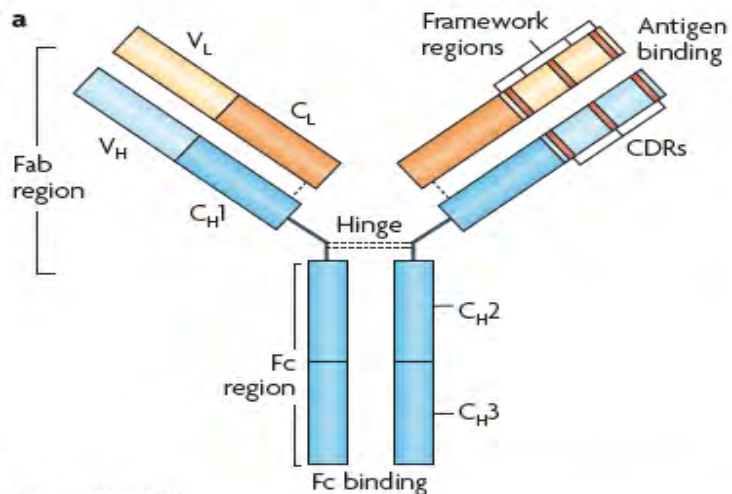


Mammalian cell lines

CHO (*Chinese hamster ovary*)

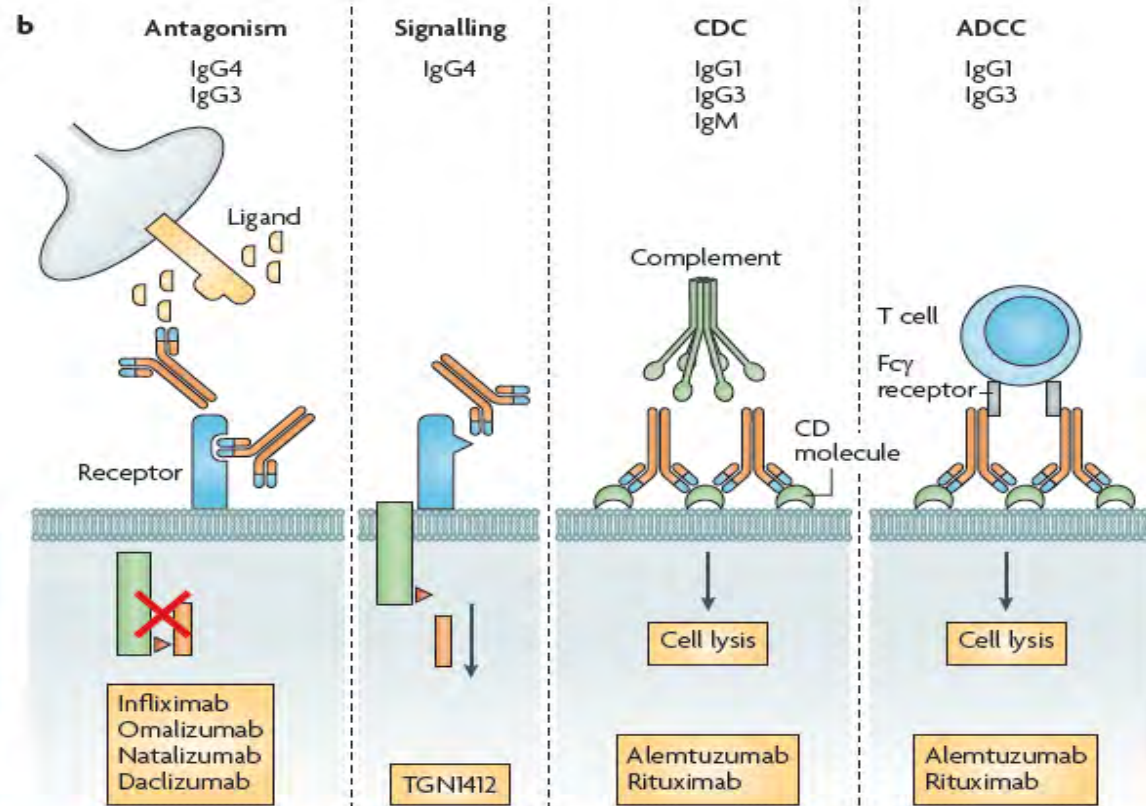
NSO (*murine myeloma*)

cell



Types of mAbs

Murine	Entirely murine amino acids	'o' = mouse e.g. mur <u>o</u> monab
Chimeric	Human constant (C) + murine variable (V) regions	'xi' = chimeric e.g. ritux <u>i</u> mab
Humanized	Murine complementarity determining regions (CDRs)	'zu' = humanized e.g. alemtu <u>z</u> umab
Human	Entirely human amino acids	'u' = human e.g. adalimu <u>u</u> mab

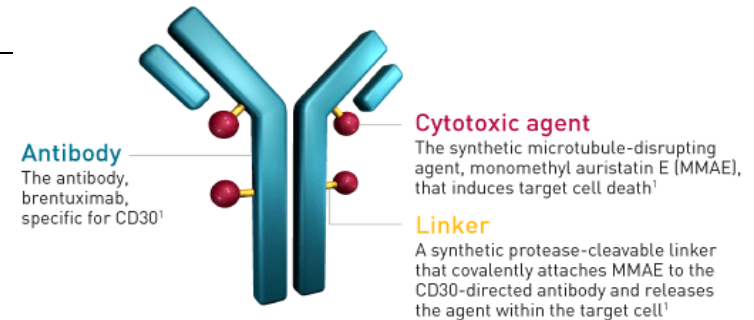


19 July 2012
EMA/CHMP/471107/2012
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion¹ (initial authorisation)

Adcetris

Brentuximab vedotin



On 19 July 2012, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for the medicinal product Adcetris, 50 mg, powder for concentrate for solution for infusion, intended for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): (1) following autologous stem cell transplant (ASCT) or (2) following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option as well as for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

Adcetris was designated as an orphan medicinal product on 15 January 2009. The applicant for this medicinal product is Takeda Global Research and Development Centre (Europe) Ltd. They may request a re-examination of any CHMP opinion, provided they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

Brentuximab Vedotin Mechanism of Action



Brentuximab vedotin (SGN-35) ADC

monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

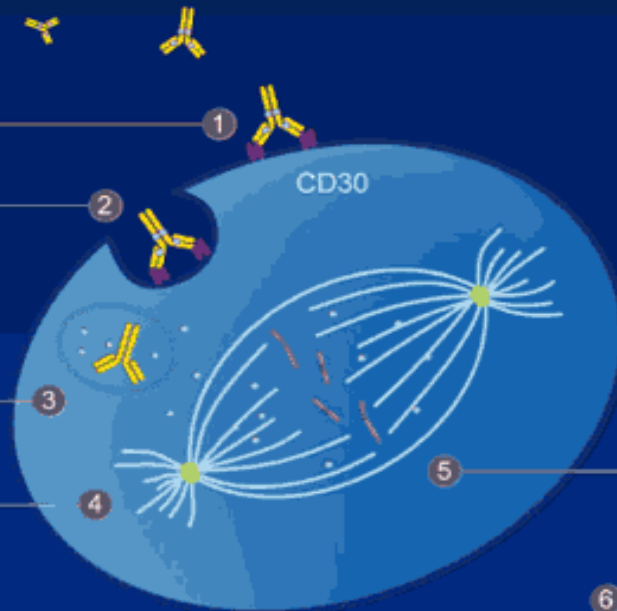
anti-CD30 monoclonal antibody

ADC binds to CD30

ADC-CD30 complex
traffics to lysosome

MMAE is released

MMAE disrupts
microtubule network



G2/M cell
cycle arrest

Apoptosis



EFFECT OF PEGYLATION ON PHARMACEUTICALS

J. Milton Harris & Robert B. Chess†*

Protein and peptide drugs hold great promise as therapeutic agents. However, many are degraded by proteolytic enzymes, can be rapidly cleared by the kidneys, generate neutralizing antibodies and have a short circulating half-life. Pegylation, the process by which polyethylene glycol chains are attached to protein and peptide drugs, can overcome these and other shortcomings. By increasing the molecular mass of proteins and peptides and shielding them from proteolytic enzymes, pegylation improves pharmacokinetics. This article will review how PEGylation can result in drugs that are often more effective and safer, and which show improved patient convenience and compliance.

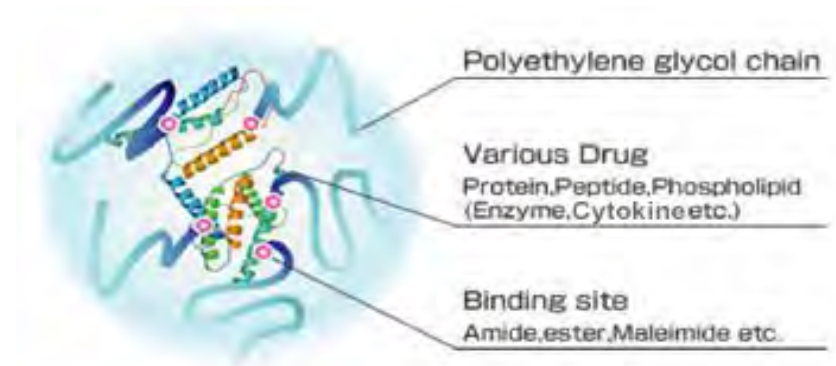
Pegasys (PEG-IFN α 2a)

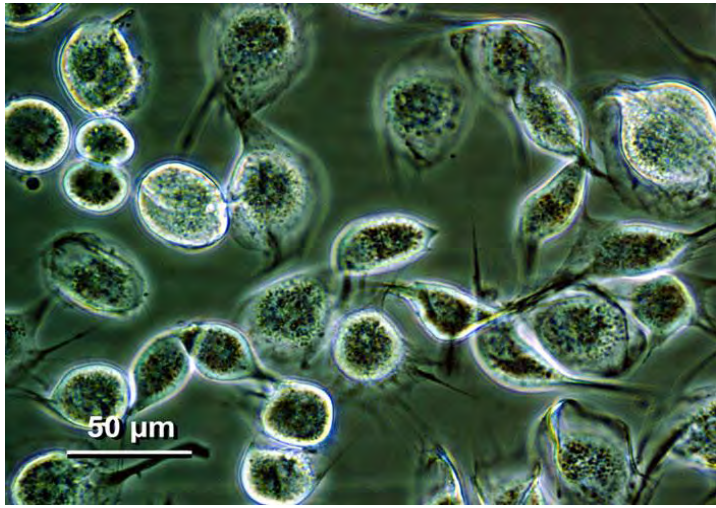
PegIntron (PEG-IFN α 2b)

Mircera (PEG-EPO)

Plegridy (PEG-IFN beta-1a)

Adynovi (PEG-FVIII)





Recombinant baculovirus
expression system and the
insect cell line Hi-5 Rix4446
derived from
Trichoplusia ni



Belated approval of first recombinant protein from animal

In June, the London-based European Medicines Agency (EMA) announced approval of the first drug produced in an animal bioreactor: GTC Biotherapeutics' ATryn, four months after its initial rejection. The drug—a recombinant form of human antithrombin produced in goats—prevents blood clots in patients who lack the natural anticoagulant protein. Industry insiders believe that EMA altered its position, after a more detailed review of the data, because it wanted to convey its support to industry for this bioprocessing method.

EMA's positive opinion, announced on June 2, 2006, overturns the agency's rejection of ATryn last February. ATryn is indicated for hereditary antithrombin deficiency, a rare disease afflicting just one in 3,000–5,000 people. So when GTC first approached the EMA, it could provide clinical data on just 19 cases—five surgical patients, nine pregnant women and five 'compassionate use' cases. Citing dosing inconsistencies, the EMA disqualified all but the five surgical cases, leaving a number far below the minimum 12 cases



The first recombinant protein produced in goat bioreactor ATryn received a belated approval from the European Union in June after an initial rejection.

ATryn's approval gives a welcome boost to this industry sector, said Phillip Nadeau, a biotech analyst with Cowen & Co. in New York. "Before this decision, pessimists believed regulatory authorities would always find a way to shoot down transgenic proteins," he said. "But now that we have an approval, that argument goes away."

Although he won't disagree, Louis Marie

competitor—Pharming, a Dutch company working with rabbits—rose nearly 10%, reflecting a broader impact on investor confidence. "It really confirms the regulator's validation of the technology," says Samir Sinjh, Pharming's chief business officer. Sinjh also emphasizes that regulators respond more favorably to transgenic proteins developed for unmet needs.

The sector still faces some difficult challenges, however. Regulatory agencies, Sinjh stresses, need assurance that transgenic proteins are safe, and this creates burdensome data requirements. The biggest safety concerns, according to Amy Rosenberg, supervisory medical officer

with the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research, fall into four categories: infection (including prion infection for transgenics made in cattle); allergenic responses, immunogenic responses and autoimmune reactions arising should transgenic proteins break tolerance to their endogenous, self-protein counterparts. "We would really need assurance that the



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2010
EMA/CHMP/380794/2010
Committee for medicinal products for human use (CHMP)

Summary of opinion¹ (initial authorisation)

Ruconest conestat alfa



On 24 June 2010 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Ruconest, 2100 U, powder for solution for injection intended for the **treatment of hereditary angioedema**. Ruconest was designated as an **orphan medicinal product on 11 May 2001**. The applicant for this medicinal product is Pharming Group N.V.

They may request a re-examination of any CHMP opinion, provided they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

The active substance of Ruconest, **conestat alfa (ATC Code not yet assigned), is a recombinant human component 1 (C1) esterase inhibitor**. C1-inhibitor controls the activation of certain proteins in the complement, coagulation, fibrinolytic and contact systems that are involved in inflammation. Patients with hereditary angioedema (HAE) caused by C1 inhibitor deficiency experience recurrent attacks of angioedema. Replacement therapy with Ruconest relieves the symptoms and reduces the duration of these attacks. The most common side effect from taking Ruconest is headache.



'Pharmers' hope for first plant drug harvest

An approval by the US Food and Drug Administration later this month for Protalix/Pfizer's plant-derived human therapeutic protein taliglucerase alfa would mark a first for 'pharmers'.

Alisa Opar

Carrots are good for us, according to popular wisdom. That saying could soon take on new meaning for people with Gaucher's disease, a rare genetic lysosomal storage disorder in which the body does not produce enough glucocerebrosidase. Later this month, the US Food and Drug Administration (FDA) is widely anticipated to approve taliglucerase alfa (Pfizer/Protalix), a recombinant form of human glucocerebrosidase that is produced in genetically engineered carrot cells.

If given the green light, on or before its Prescription Drug User Fee Act action date of 25 February, the enzyme-replacement therapy will be the first FDA-approved plant-derived human therapeutic protein. "An approval for taliglucerase alfa would be a huge step forward, because it validates this new plant-based platform for producing biologics. It opens the door for everybody," says Joe Boothe, the Vice President of Research and Development at SemBioSys, which has a safflower seed-derived human insulin in Phase III development.

First in plant

Interest in 'pharming' took off in the early 1990s after researchers showed that monoclonal antibodies could be made in tobacco plants (*Nature*, 342, 76-78, 1989). In subsequent years companies began to genetically engineer plants, or plant cells, to produce vaccines, antibodies and proteins for therapeutics.

Despite initial promises, including reduced manufacturing costs, it has been slow growing for plant-based pharming. The production of drugs outdoors in corn and tobacco fuelled public fears that they would taint

FDA approval May 2012



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2015
EMA/514387/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kanuma

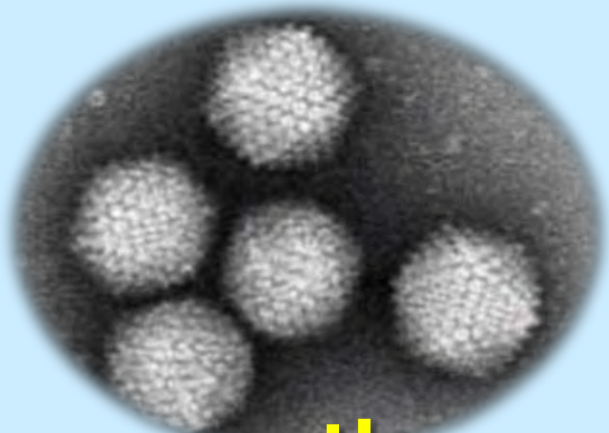
International non-proprietary name: sebelipase alfa



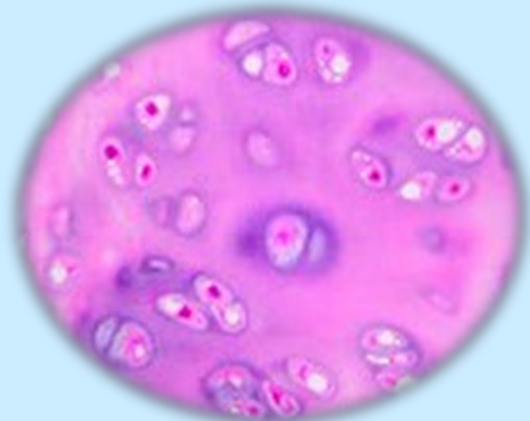
The active substance, sebelipase alfa, is a recombinant form of human lysosomal acid lipase (hLAL). This enzyme catalyzes the hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids and is as such involved in the maintenance of a normal lipid metabolism. It is the first recombinant product expressed in transgenic chicken (*Gallus gallus*) and purified from egg white of transgenic hens.

The finished product is presented as a sterile liquid concentrate for injection intended for single use intravenous infusion containing 20 mg (2 mg/mL) of the active substance sebelipase alfa. Prior to intravenous administration, the finished product is diluted with 0.9% sodium chloride injection USP/Ph. Eur.

ATMP in the EU



gene therapy



cell therapy



tissue engineering

Regulation (EC) No 1394/2007

10.12.2007

EN

Official Journal of the European Union

L 324/121

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC
and Regulation (EC) No 726/2004

(Text with EEA relevance)

Specific rules regarding the

**authorization
supervision
pharmacovigilance**

of advanced therapy medicinal products (ATMPs)

Directive 2009/120/EC

Gene therapy medicinal product

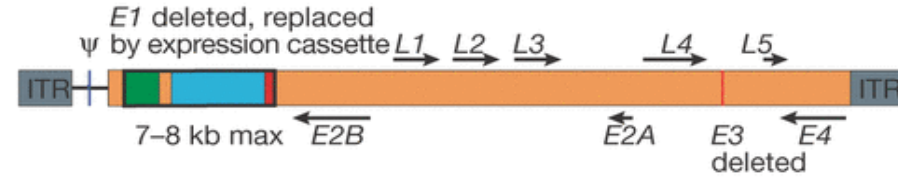
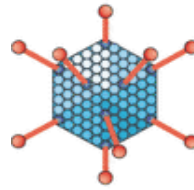
Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

- (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.

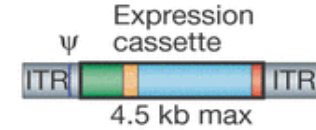
Gene therapy medicinal products shall not include vaccines against infectious diseases.

viral vectors

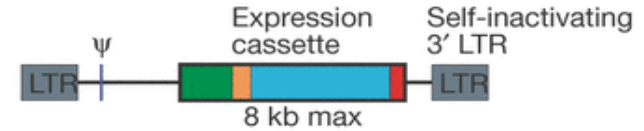
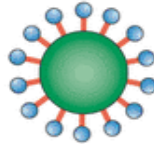
Adenovirus (~36 kb genome)



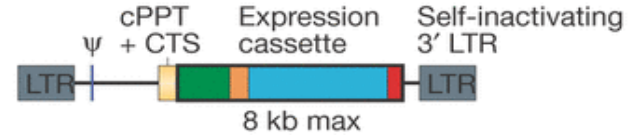
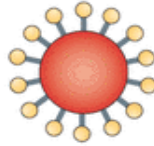
Adeno-associated virus (4.7 kb genome)



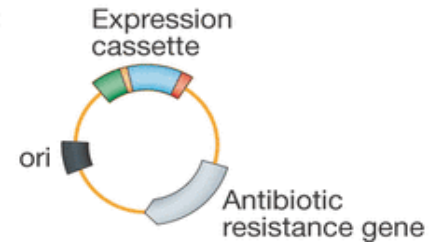
Retrovirus (7–10 kb genome)



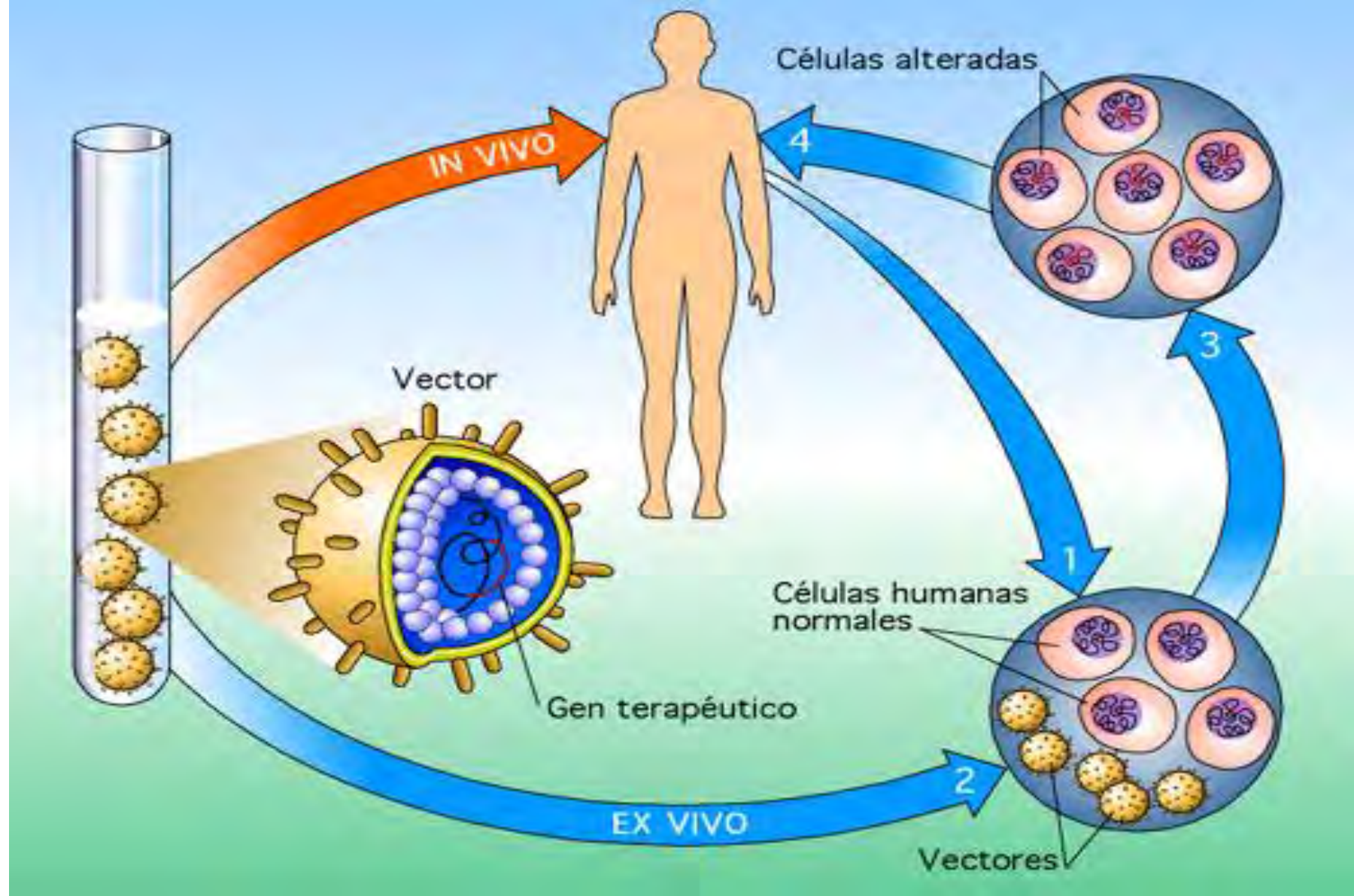
Lentivirus (9–10 kb genome)

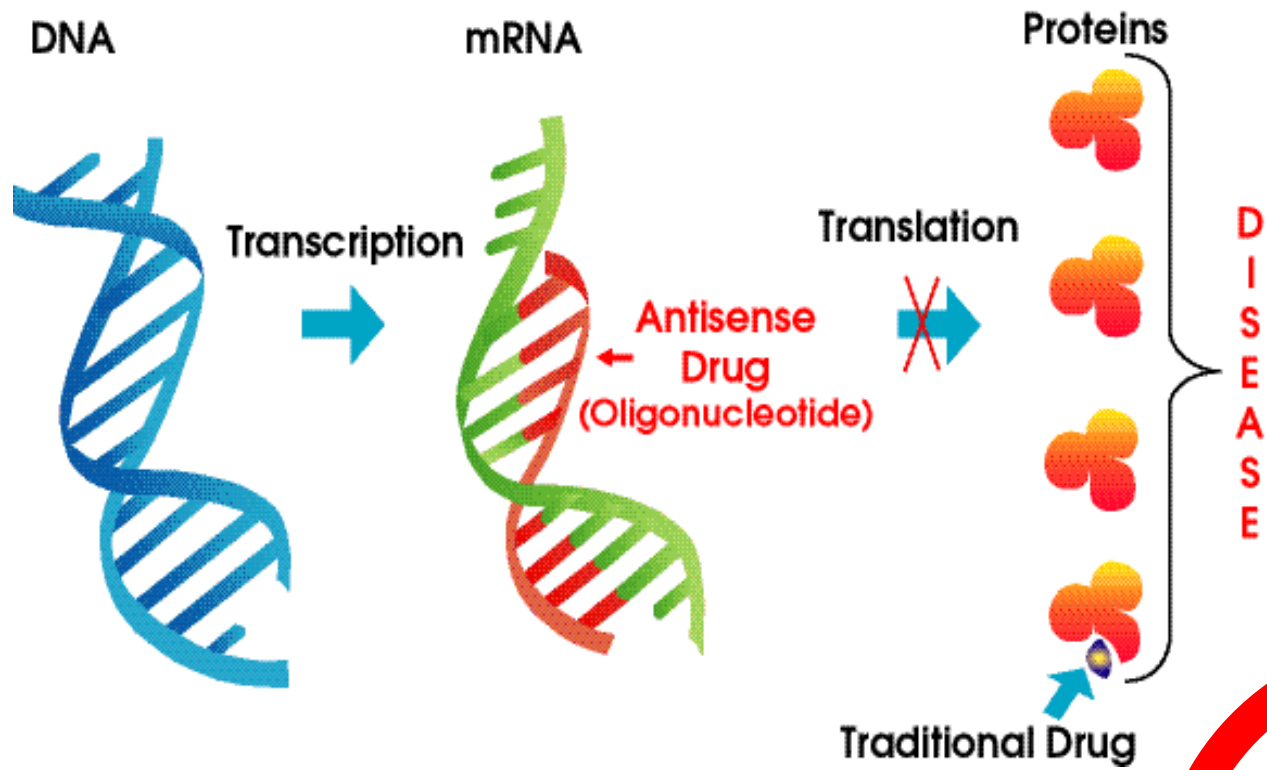


Liposome + plasmid (unlimited sized genome)

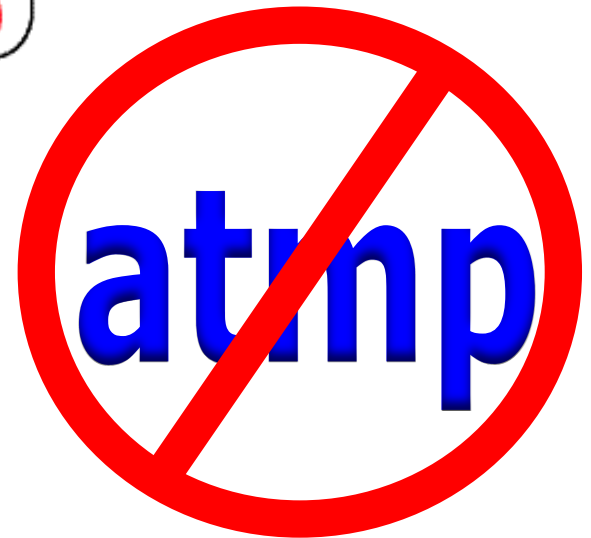


non-viral vectors

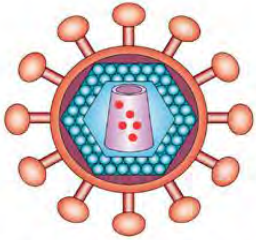




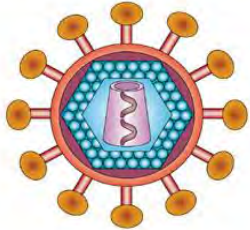
antiVEGF	Structure	Target	Vitreous (wk)
Macugen (Pegaptanib)	RNA aptamer	VEGF165 isoform	6



HIV

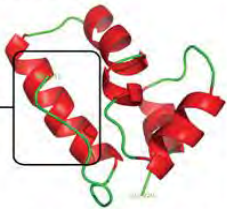


Whole inactivated

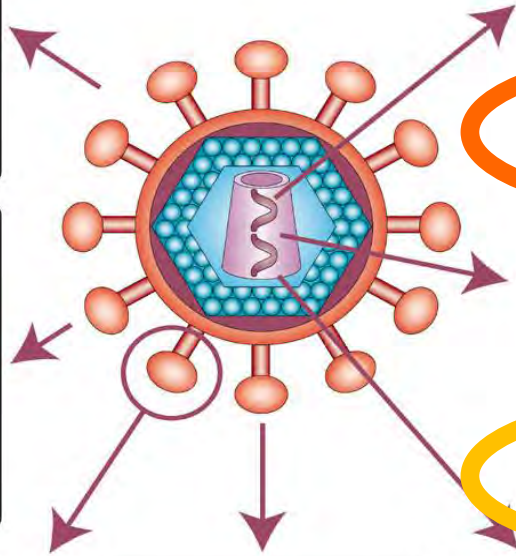


Live attenuated

---LPQPGGSYC---



Synthetic peptides



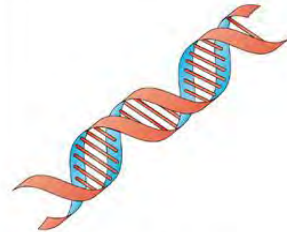
Recombinant viral vectors



Recombinant bacterial vectors



Recombinant subunit



DNA



Gene therapy clinical trials worldwide to 2012 – an update

Samantha L. Ginn^{1,2}

Ian E. Alexander^{1,3}

Michael L. Edelstein⁴

Mohammad R. Abedi⁵

Jo Wixon^{6*}

¹Gene Therapy Research Unit,
Children's Medical Research Institute
and The Children's Hospital at
Westmead, NSW, Australia

²Sydney Medical School, University of
Sydney, NSW, Australia

³Discipline of Paediatrics and Child
Health, University of Sydney, NSW,
Australia

⁴Imperial Healthcare NHS Trust,
London, UK

⁵Department of Laboratory Medicine,
Örebro University Hospital, Örebro,
Sweden

Abstract

To date, over 1800 gene therapy clinical trials have been completed, are ongoing or have been approved worldwide. Our database brings together global information on gene therapy clinical trials from official agency sources, published literature, conference presentations and posters kindly provided to us by individual investigators or trial sponsors.

This review presents our analysis of clinical trials that, to the best of our knowledge, have been or are being performed worldwide. As of our June 2012 update, we have entries on 1843 trials undertaken in 31 countries. We have analysed the geographical distribution of trials, the disease indications (or other reasons) for trials, the proportions to which different vector types are used, and which genes have been transferred. Details of the analyses presented, and our searchable database are available on *The Journal of Gene Medicine* Gene Therapy Clinical Trials Worldwide website at: <http://www.wiley.co.uk/genmed/clinical>. We also provide an overview of the progress being made in clinical trials of gene therapy approaches around the world and discuss the prospects for the future. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords clinical trials; gene therapy; *The Journal of Gene Medicine*; worldwide;

Table 1. Conditions for which human gene transfer trials have been approved

Monogenic disorders

Adrenoleukodystrophy
 α -1 antitrypsin deficiency
 Becker muscular dystrophy
 β -thalassaemia
 Canavan disease
 Chronic granulomatous disease
 Cystic fibrosis
 Duchenne muscular dystrophy
 Fabry disease
 Familial adenomatous polyposis
 Familial hypercholesterolaemia
 Fanconi anaemia
 Galactosialidosis
 Gaucher's disease
 Gyrate atrophy
 Haemophilia A and B
 Hurler syndrome
 Hunter syndrome
 Huntington's chorea
 Junctional epidermolysis bullosa
 Late infantile neuronal ceroid lipofuscinosis
 Leukocyte adherence deficiency
 Limb girdle muscular dystrophy
 Lipoprotein lipase deficiency
 Mucopolysaccharidosis type VII
 Ornithine transcarbamylase deficiency
 Pompe disease
 Purine nucleoside phosphorylase deficiency
 Recessive dystrophic epidermolysis bullosa
 Sickle cell disease
 Severe combined immunodeficiency
 Tay Sachs disease
 Wiskott–Aldrich syndrome

Cancer

Gynaecological – breast, ovary, cervix, vulva
Nervous system – glioblastoma, leptomeningeal carcinomatosis, glioma, astrocytoma, neuroblastoma, retinoblastoma
Gastrointestinal – colon, colorectal, liver metastases, post-hepatitis liver cancer, pancreas, gall bladder
Genitourinary – prostate, renal, bladder, anogenital neoplasia
Skin – melanoma (malignant/metastatic)
Head and neck – nasopharyngeal carcinoma, squamous cell carcinoma, oesophageal cancer
Lung – adenocarcinoma, small cell/nonsmall cell, mesothelioma
Haematological – leukaemia, lymphoma, multiple myeloma
Sarcoma
Germ cell
Li–Fraumeni syndrome
Thyroid

Neurological diseases

Alzheimer's disease
 Amyotrophic lateral sclerosis
 Carpal tunnel syndrome
 Cubital tunnel syndrome
 Diabetic neuropathy
 Epilepsy
 Multiple sclerosis
 Myasthenia gravis
 Parkinson's disease
 Peripheral neuropathy
 Pain

Ocular diseases

Age-related macular degeneration
 Diabetic macular edema
 Glaucoma
 Retinitis pigmentosa
 Superficial corneal opacity

Ompe disease
Purine nucleoside phosphorylase deficiency
Recessive dystrophic epidermolysis bullosa
Sickle cell disease
Severe combined immunodeficiency
Tay Sachs disease
Wiskott–Aldrich syndrome

Cardiovascular disease

Anaemia of end stage renal disease
Angina pectoris (stable, unstable, refractory)
Coronary artery stenosis
Critical limb ischaemia
Heart failure
Intermittent claudication
Myocardial ischaemia
Peripheral vascular disease
Pulmonary hypertension
Venous ulcers

Infectious disease

Adenovirus infection
Cytomegalovirus infection
Epstein–Barr virus
Hepatitis B and C
HIV/AIDS
Influenza
Japanese encephalitis
Malaria
Paediatric respiratory disease
Respiratory syncytial virus
Tetanus
Tuberculosis

Ocular diseases

Age-related macular degeneration
Diabetic macular edema
Glaucoma
Retinitis pigmentosa
Superficial corneal opacity
Choroideraemia
Leber congenital amaurosis

Inflammatory diseases

Arthritis (rheumatoid, inflammatory, degenerative)
Degenerative joint disease
Ulcerative colitis
Severe inflammatory disease of the rectum

Other diseases

Chronic renal disease
Erectile dysfunction
Detrusor overactivity
Parotid salivary hypofunction
Oral mucositis
Fractures
Type I diabetes
Diabetic ulcer/foot ulcer
Graft versus host disease/transplant patients

Directive 2009/120/EC

Somatic cell therapy medicinal product

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

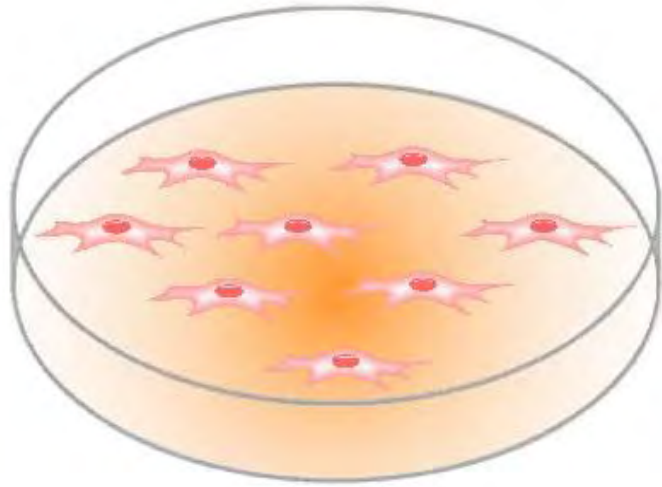
- (a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;
- (b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

Regulation (EC) No 1394/2007

Tissue engineered product means a product that:

- contains or consists of engineered cells or tissues, and
- is administered to human beings with a view to regenerating, repairing or replacing a human tissue

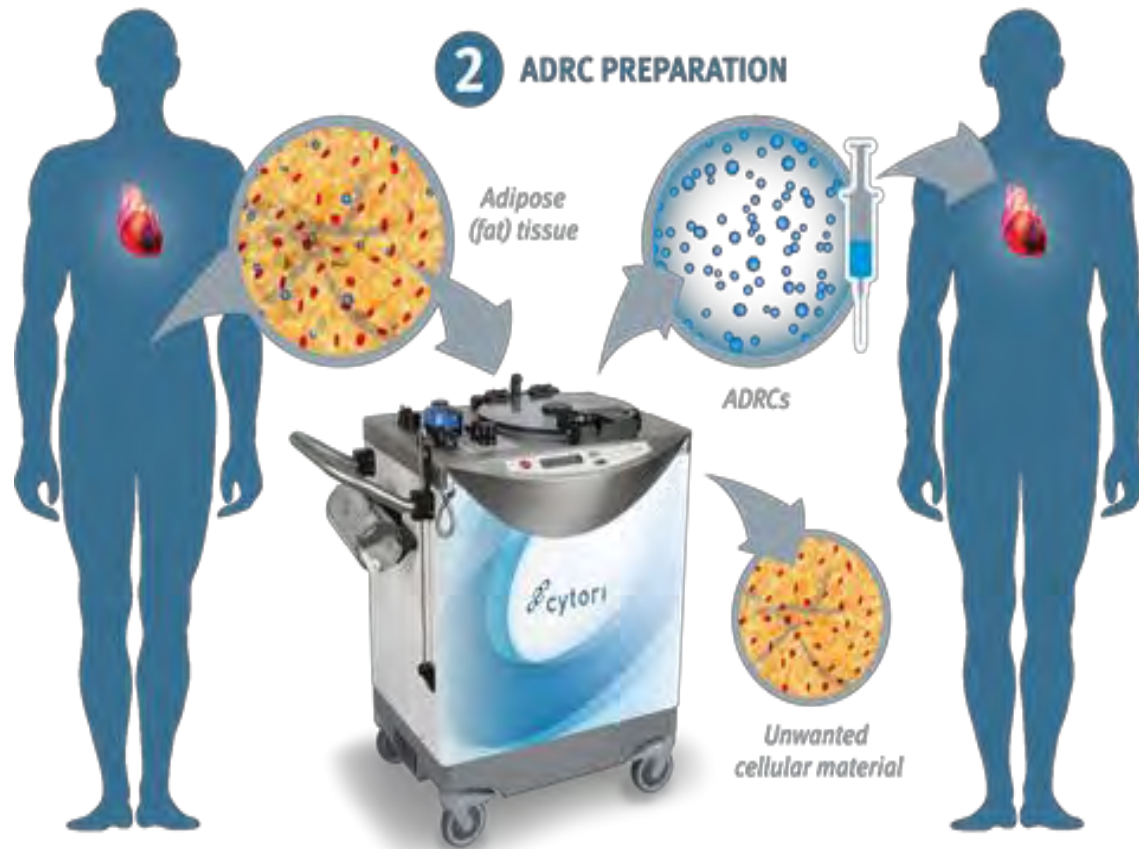


atmp

1 LIPOSUCTION

2 ADRC PREPARATION

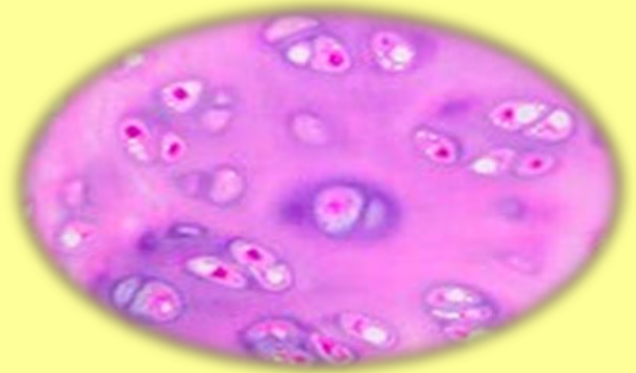
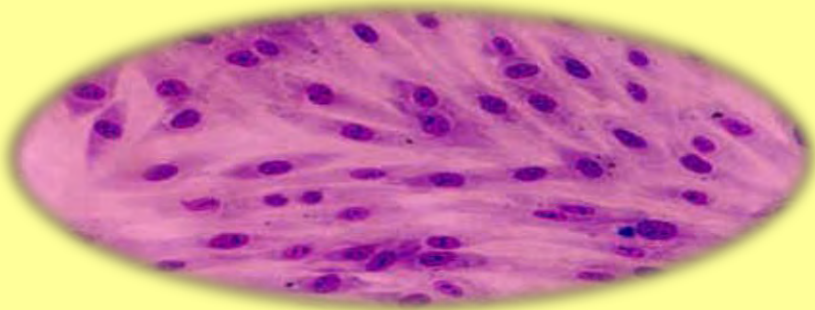
3 ADRC INJECTION



atmp

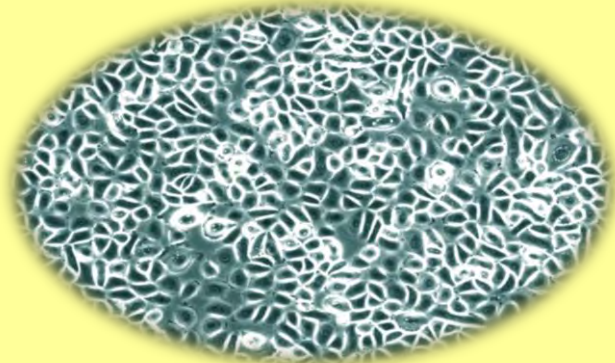
“established therapies”

chondrocytes

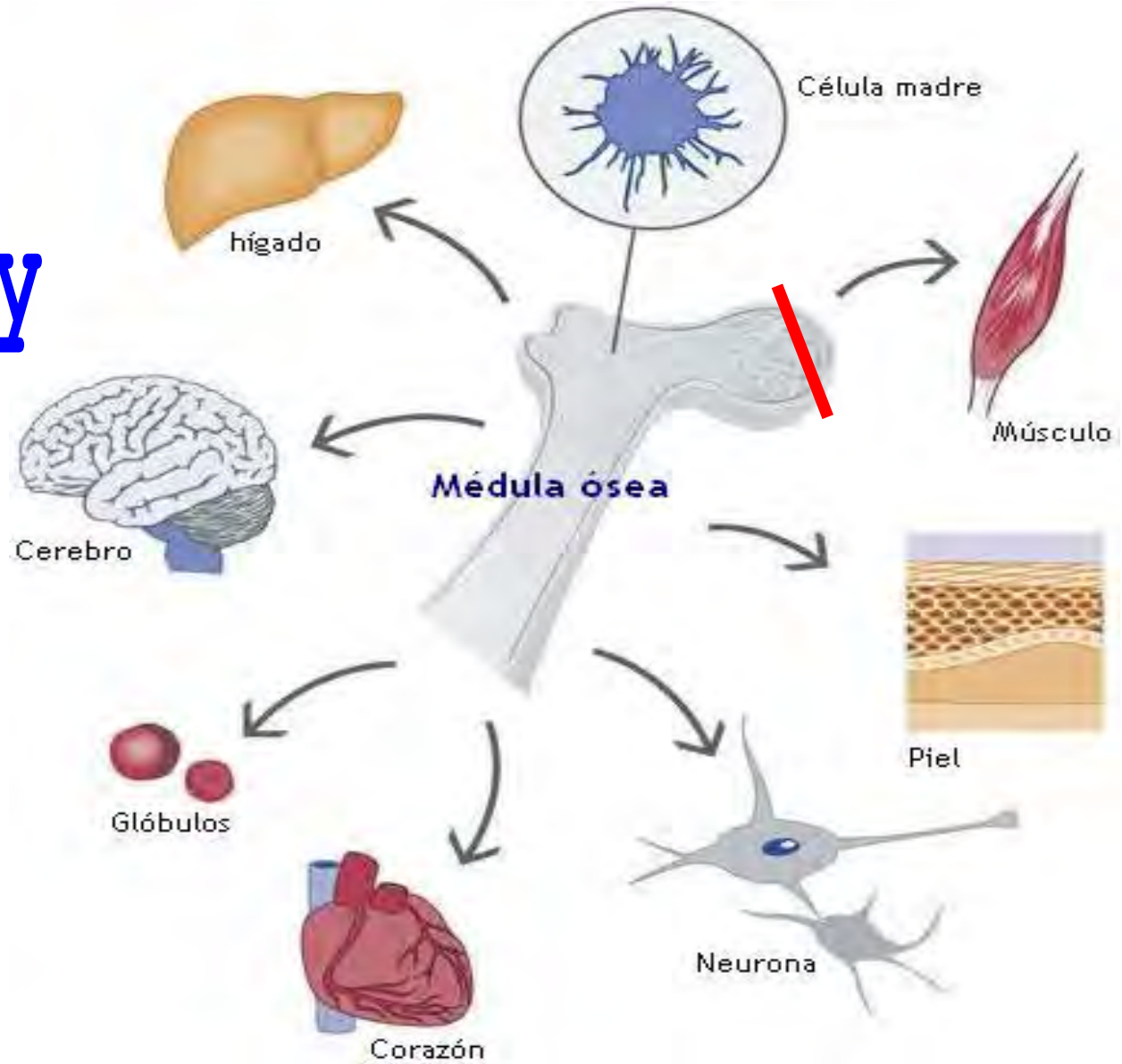


keratinocytes

limbal stem cells



cell therapy



CAT Classification

- **Is the product classified as ATMP?**
- **Is it classified as TEP, somatic cell therapy, or gene therapy medicinal product?**
- **Is it combined or non-combined?**
- **Classification is**
 - **voluntary**
 - **free of charge**
 - **not legally binding**



Overview

Research and
development

▼ Marketing
authorisation

▼ Advanced therapies

▼ Advanced therapy
classification

Summaries of
advanced therapy
classification

Marketing
authorisation

Accelerated
assessment

Biosimilars

► Home ► Human regulatory ► Marketing authorisation ► Advanced therapies ► Advanced therapy classification

Advanced therapy classification

Companies can consult the European Medicines Agency (EMA) to determine whether a medicine they are developing is an advanced therapy medicinal product (ATMP). The procedure allows them to receive confirmation that a medicine, which is based on genes, cells or tissues, meets the scientific criteria for defining an ATMP.

The criteria for ATMPs are set out in Article 17 of [Regulation \(EC\) No 1394/2007](#). The classification procedure is optional.

EMA established the procedure to address questions on **borderline classification** with other areas, such as medical devices, as early as possible.

EMA's [Committee for Advanced Therapies \(CAT\)](#) delivers scientific recommendations on ATMP classification after consultation with the European Commission within 60 days after receipt of the request.

EMA **publishes the outcome** of the assessment of the classification of ATMPs as summary reports:

Overview
Research and development
Marketing authorisation
Advanced therapies
Advanced therapy classification
Summaries of advanced therapy classification
Marketing authorisation
Accelerated assessment
Biosimilars
Compliance
Clinical data publication
Conditional marketing authorisation
Data on medicines (ISO IDMP standards)
Generic medicines
Guidance documents
Orphan medicines
Medicines for use outside EU (Article 58)

Summaries of scientific recommendations on classification of advanced therapy medicinal products





[Email](#)
[Print](#)
[Help](#)
[Share](#)

The European Medicines Agency's Committee for Advanced Therapies delivers scientific recommendations on whether a medicine can be classified as an advanced therapy medicinal product (ATMP). The Agency publishes the outcomes of these assessments in the format of summary reports.

Summary reports are available for classification recommendations from July 2011.

For more information, see

- [Classification of ATMPs](#)
- [Committee for Advanced Therapies](#)

Product description	Therapeutic area	Classification	Date of adoption of recommendation
 Haematopoietic stem cells genetically modified to express a zinc finger nuclease which disrupts the enhancer of BCL11A expression	Intended for the treatment of β -thalassaemia	Gene therapy <u>medicinal product</u>	21/04/2016
 Human burn eschar and debrided adipose tissue cells (suspension)	Intended for the treatment of burns, scars, non-healing wounds	Tissue engineered product	23/03/2016
 Human burn eschar and debrided adipose tissue cells (sheet)	Intended for the treatment of burns, scars, non-healing wounds	Tissue engineered product	23/03/2016
 Human burn eschar and debrided adipose tissue cells (on acellular amniotic matrix)	Intended for the treatment of burns, scars, non-healing wounds	Tissue engineered product	23/03/2016

advanced therapy medicinal products

SHOULD COMPLY WITH THE LEGISLATION FOR MED PROD

- their use needs to be authorized: marketing authorization, clinical **study**, **compassionate use**...
- quality, safety and efficacy
- **GMP** (production & control), **GLP** (non-clinical) and **GCP** (clinical studies) apply



- clinical studies, compassionate use
- *hospital exemption*



MA in the EU
(centralized procedure)

SCOPE

Advanced therapy medicinal products which are intended to be placed on the market in Member States and either **prepared industrially** or manufactured by a method involving an **industrial process** (Title II of Directive 2001/83).

Advanced Therapy Medicinal Products

Regulation (EC) 1394/2007

- Marketing authorisation required
- Demonstration of Q, S & E
- Post-authorisation vigilance of **S & E**
- **Centralised procedure mandatory**



**C
E
N
T
R
A
L
I
Z
E
D**
**P
R
O
C
E
D
U
R
E**

european medicines agency

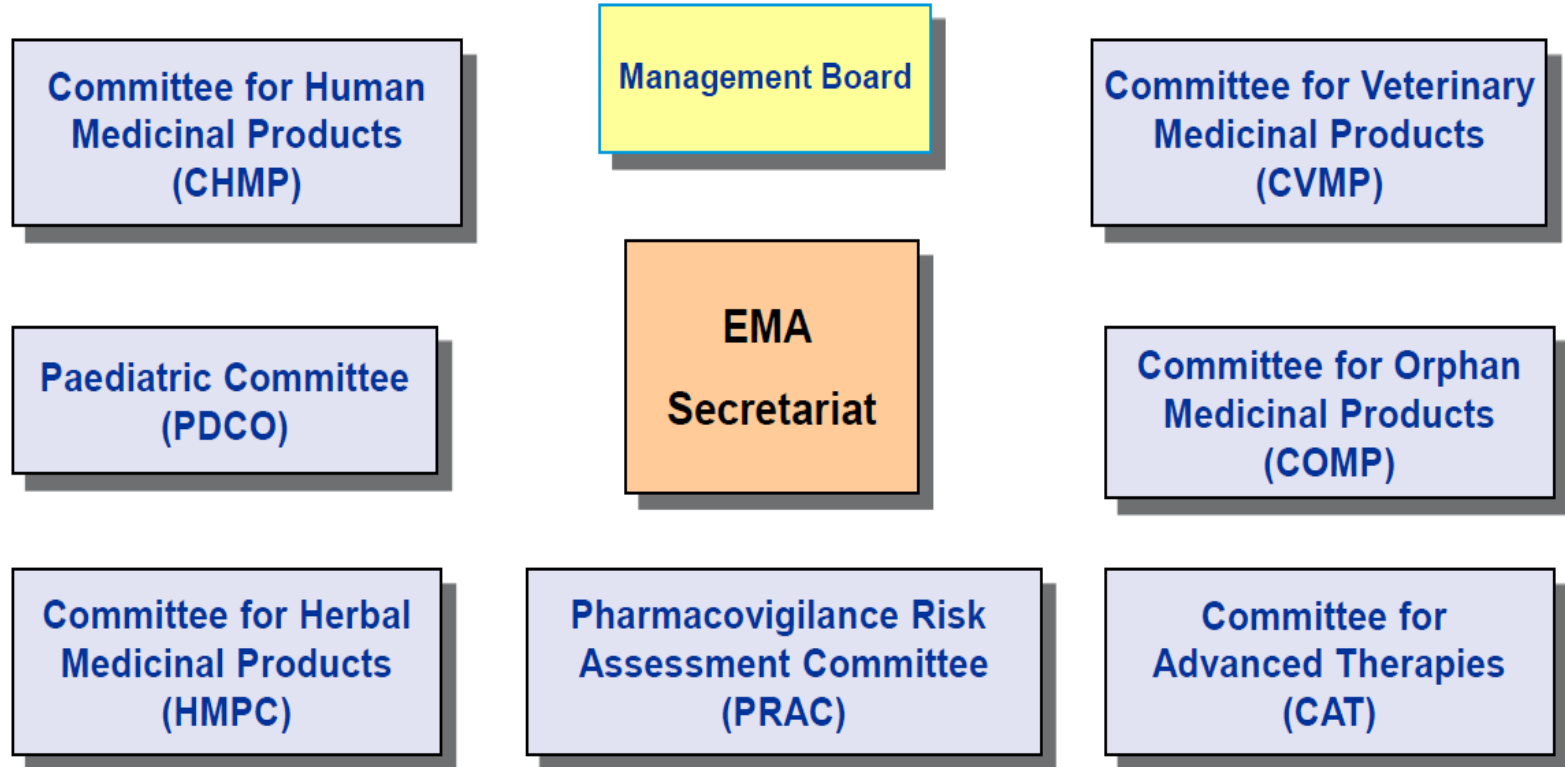
A single
MA in the
EU

210-d
evaluation
process

Same
indications
& SmPC

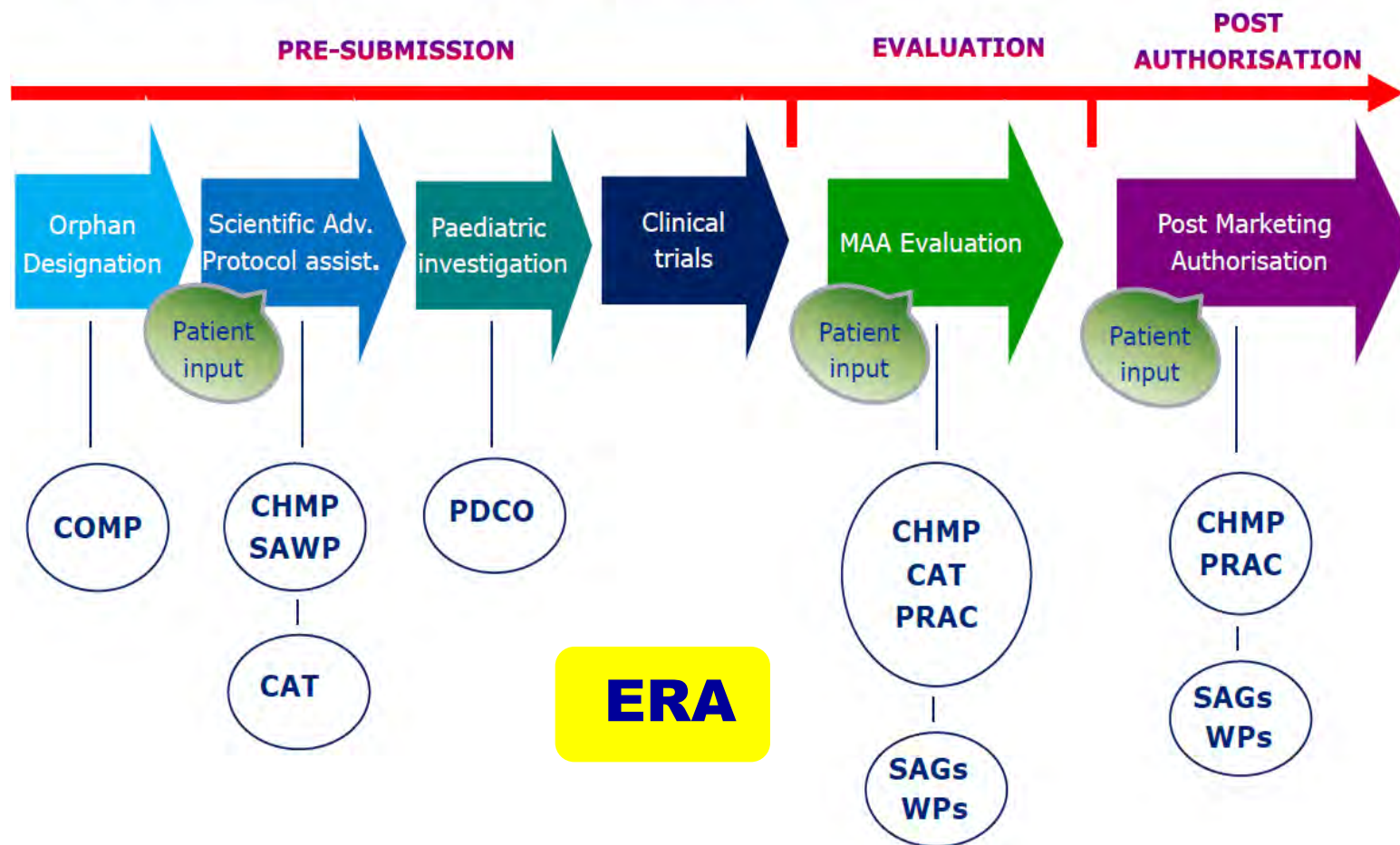
**Price and reimbursement
decided by each member
state**

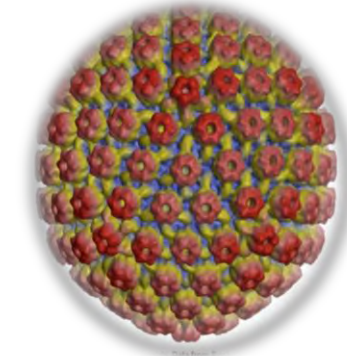






Centralised procedure - product life-cycle





maa

bwp

QUALITY

cat

DRAFT OPINION

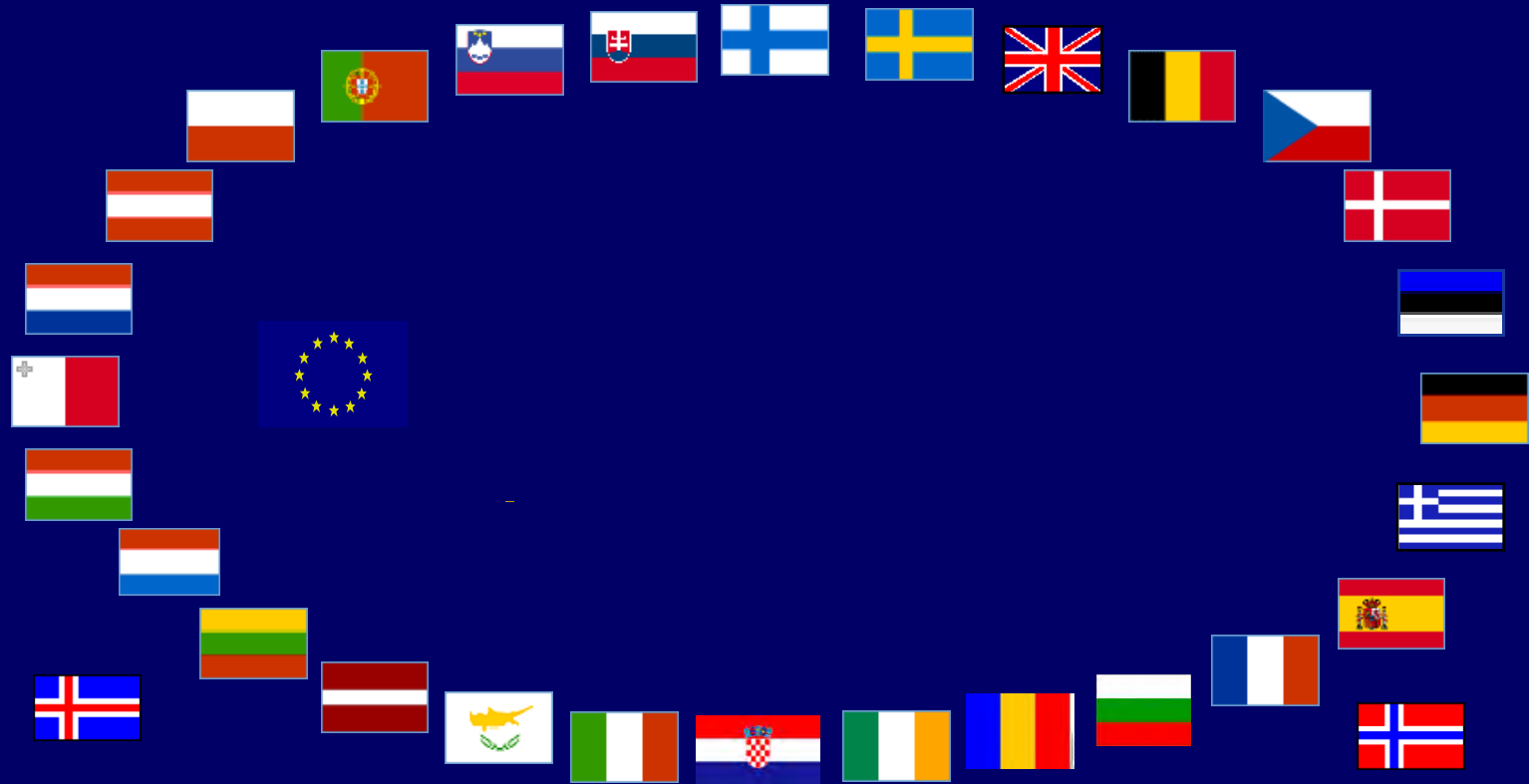
prac

RMP

chmp

OVERALL FINAL OPINION

CHMP



- 1 member per MS (+1 alt) - 28
- 1 member from NO and ICE (+1 alt) (observers)
- 5 co-opted members (elected by the CHMP)

**FINAL opinion on ALL
medicines for HUMAN use**

5. BENEFIT RISK ASSESSMENT

Benefits|

Beneficial effects

Uncertainty in the knowledge about the beneficial effects

Risks

Unfavourable effects

Uncertainty in the knowledge about the unfavourable effects

Balance

Importance of favourable and unfavourable effects

Benefit-risk balance

Discussion on the benefit-risk assessment

5.1. Conclusions

The overall B/R of <name of product> <is> <positive> provided <general statement on conditions>;
is <negative>.

Committees, working parties and other groups

[Email](#) [Print](#) [Help](#) [Share](#)

The European Medicines Agency has seven scientific committees and a number of working parties and related groups which conduct the scientific work of the Agency.

In this section

- ▶ [How the committees work](#)
- ▶ [Committee for Medicinal Products for Human Use \(CHMP\)](#)
- ▶ [Pharmacovigilance Risk Assessment Committee \(PRAC\)](#)
- ▶ [Committee for Medicinal Products for Veterinary Use \(CVMP\)](#)
- ▶ [Committee for Orphan Medicinal Products \(COMP\)](#)
- ▶ [Committee on Herbal Medicinal Products \(HMPC\)](#)
- ▶ [Committee for Advanced Therapies \(CAT\)](#)
- ▶ [Paediatric Committee \(PDCO\)](#)
- ▶ [Working parties and other groups](#)

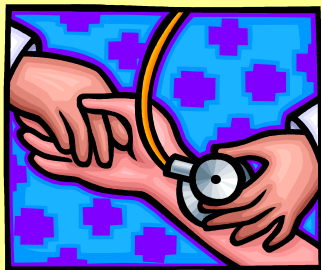




EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

atmp centralized procedure

CHmp



Human Med

draft opinion



cat



final opinion

07/2009	CHONDROSELECT	<i>Autologous chondrocytes</i>
07/2012	GLYBERA	<i>AAV-LPL</i>
04/2013	MACI	<i>Matrix-induced autologous chondrocyte implantation</i>
06/2013	PROVENGE	<i>Autologous PBMC activated with PAP-GM-CSF</i>
12/2014	HOLOCLAR	<i>Autologous human corneal epithelial cells</i>
10/2015	IMLYGIC	<i>Oncolytic HSV-1 - GM-CSF</i>
04/2016	STRIMVELIS	<i>Autologous CD34+ - RV hu ADA</i>
06/2016	ZALMOXIS	<i>T cells - HSV-TK</i>
05/2017	SPHEROX	<i>Spheroids of human autologous matrix-associated chondrocytes</i>
12 / 2017	ALOFISEL	<i>Allogeneic expanded adipose stem cells</i>

► [News and press releases](#)[Events](#)[What's new](#)[Committee highlights](#)[Therapeutic areas:
latest updates](#)[Medicine evaluation
figures](#)[Publications](#)[Press and social media](#)[Open consultations](#)[RSS feeds](#)[► Home](#) [► News and Events](#) [► News and press releases](#)

New medicine to treat perianal fistulas in patients with Crohn's disease

[✉ Email](#) [🖨 Print](#) [🔗 Help](#) [📱 Share](#)

Press release

15/12/2017

New medicine to treat perianal fistulas in patients with Crohn's disease

Alofisel is the tenth advanced therapy recommended for marketing authorisation

The European Medicines Agency (EMA) has recommended granting a marketing authorisation in the European Union (EU) for a new advanced therapy medicinal product (ATMP) for the treatment of complex perianal fistulas in patients with Crohn's disease. Alofisel is the tenth ATMP that has received a positive opinion from the Agency's Committee for Medicinal Products for Human Use (CHMP).

Crohn's disease is a long-term condition that causes inflammation of the digestive system or gut. Apart from affecting the lining of the bowel, inflammation may also go deeper into the bowel wall. Perianal fistulas are common complications of Crohn's disease and occur when an abnormal passageway develops between the rectum and the outside of the body. These can lead to incontinence (a lack of control over the opening of the bowels) and sepsis (blood infection). Complex fistulas are known to be more treatment resistant than simple fistulas. There is currently no cure for Crohn's disease, so the aim of treatment is to stop the inflammatory process, relieve symptoms and avoid surgery wherever possible. Crohn's disease can affect people of all ages, with a higher incidence in the younger population.

The active substance of Alofisel is darvadstrocel. Darvadstrocel contains expanded adipose stem cells which, once activated, impair proliferation of lymphocytes and reduce the release of pro-inflammatory cytokines at inflammation sites. This immunoregulatory activity reduces inflammation and may allow the tissues around the fistula tract to heal.

Related information

[► Alofisel: Pending EC decision](#)


Related content

[► Meeting highlights from the Committee for Medicinal Products for Human Use \(CHMP\) 11-14 December 2017](#)

Contact point:

EMA Press office

Tel. +44 (0)20 3660 8427

E-mail: press@ema.europa.euFollow us on Twitter [@EMA_News](#) 

07/2007

CEREPRO

AdV-HSVtk

12/2008

ADVEXIN

AdV-p53

01/2013

**HYALOGRAFT C
AUTOGRAFT**

Autologous chondrocytes

03/2013

ORANERA

*Autologous oral mucosal epithelial
cells*

10/2015

HEPARESC

Human heterologous liver cells

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

f SHARE

🐦 TWEET

in LINKEDIN

📌 PIN IT

✉ EMAIL

🖨 PRINT

**For Immediate
Release**

August 30, 2017

Release

This release was updated on Aug. 30, 2017 to correctly identify the FDA designations granted to Kymriah.

Español

The U.S. Food and Drug Administration issued a historic action today making the first gene therapy available in the United States, ushering in a new approach to the treatment of cancer and other serious and life-threatening diseases.

The FDA approved Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL).

"We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer," said FDA Commissioner Scott Gottlieb, M.D. "New technologies such as gene and cell therapies hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses. At the FDA, we're committed to helping expedite the development and review of groundbreaking treatments that have the potential to be life-saving."

Kymriah, a cell-based gene therapy, is approved in the United States for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

Kymriah is a genetically-modified autologous T-cell immunotherapy. Each dose of Kymriah is a customized treatment created using an individual patient's own T-cells,

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

f SHARE

🐦 TWEET

in LINKEDIN

📌 PIN IT

✉ EMAIL

🖨 PRINT

**For Immediate
Release**

August 30, 2017

Release

1 INDICATIONS AND USAGE

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

first gene therapy available in the United States, ushering in a new approach to the treatment of cancer and other serious and life-threatening diseases.

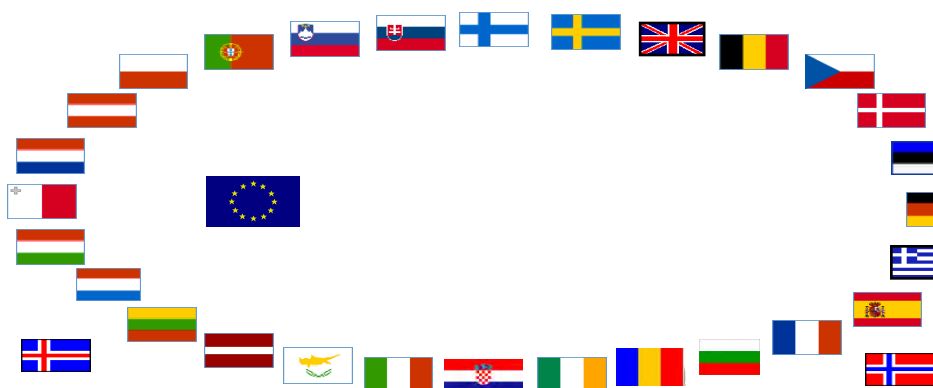
The FDA approved Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL).

"We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer," said FDA Commissioner Scott Gottlieb, M.D. "New technologies such as gene and cell therapies hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses. At the FDA, we're committed to helping expedite the development and review of groundbreaking treatments that have the potential to be life-saving."

Kymriah, a cell-based gene therapy, is approved in the United States for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

Kymriah is a genetically-modified autologous T-cell immunotherapy. Each dose of Kymriah is a customized treatment created using an individual patient's own T-cells,

CHMP



5 coopted members

Standing working parties

The current CHMP **standing working parties** are:

- ▶ Healthcare Professionals' Working Party
- ▶ **Biologics Working Party**
- ▶ Patients' and Consumers' Working Party
- ▶ Quality Working Party
- ▶ Safety Working Party
- ▶ Scientific Advice Working Party

The current CHMP temporary working parties are:

- ▶ Biosimilar Medicinal Products Working Party
- ▶ Biostatistics Working Party
- ▶ Blood Products Working Party
- ▶ Cardiovascular Working Party
- ▶ Central Nervous System Working Party
- ▶ Infectious Diseases Working Party
- ▶ Oncology Working Party
- ▶ Pharmacogenomics Working Party
- ▶ Pharmacokinetics Working Party
- ▶ Rheumatology/Immunology Working Party
- ▶ Vaccines Working Party

How the committees work

CHMP

CVMP

PRAC

COMP

HMPC

CAT

PDCO

▼ Working parties and other groups

▼ CHMP

▼ Biologics Working Party

Documents

Patients' and

[► Home](#) ►
 [Committees](#) ►
 [Working parties and other groups](#) ►
 [CHMP](#) ►
 [Biologics Working Party](#)

Biologics Working Party

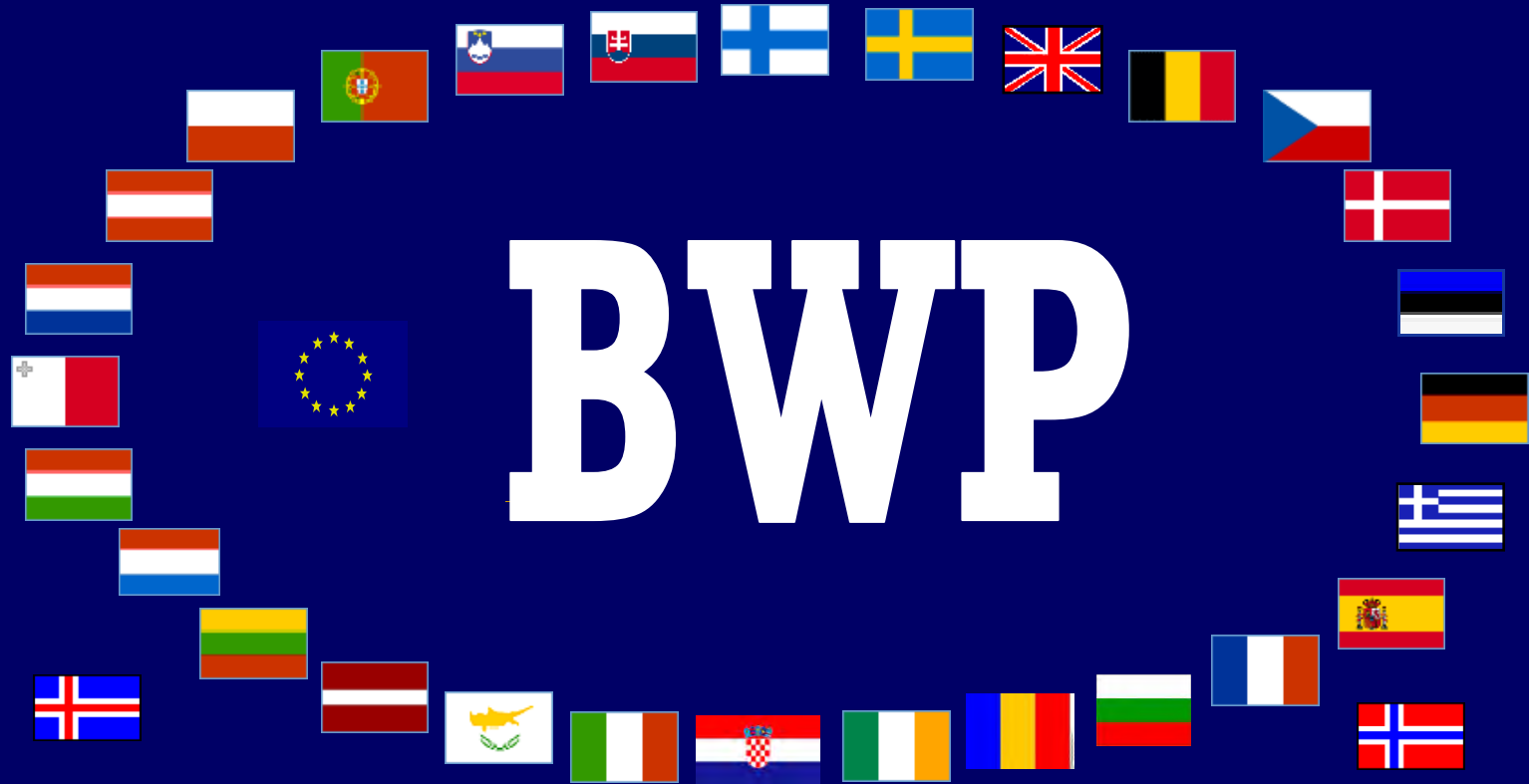
The Biologics Working Party (BWP) provides recommendations to the European Medicines Agency's [scientific committees](#) on all matters relating directly or indirectly to quality and safety aspects relating to biological and biotechnological medicines.

The BWP's tasks include:

- providing support to the [Committee for Medicinal Products for Human Use \(CHMP\)](#) on dossier evaluation, to facilitate consistency of assessments and the coherence of CHMP opinions;
- at the request of the CHMP, providing scientific advice on general and product-specific matters relating to the quality aspects of biological and biotechnological medicinal products;
- preparing, reviewing and updating guidelines, in conjunction with other appropriate working parties;
- liaising with interested parties, such as pharmaceutical industry associations, learned societies, healthcare-professional organisations and patient organisations;
- international cooperation on the quality and safety of biological and biotechnological medicinal products;
- contributing to CHMP scientific opinions in collaboration with the [World Health Organization](#) [↗](#) (WHO) for the evaluation of [medicines intended for markets outside the European Union \(EU\)](#);

- ▶ providing support to the [Committee for Medicinal Products for Human Use](#) (CHMP) on dossier evaluation, to facilitate consistency of assessments and the coherence of CHMP opinions;
- ▶ at the request of the CHMP, providing scientific advice on general and product-specific matters relating to the quality aspects of biological and biotechnological medicinal products;
- ▶ preparing, reviewing and updating guidelines, in conjunction with other appropriate working parties;
- ▶ liaising with interested parties, such as pharmaceutical industry associations, learned societies, healthcare-professional organisations and patient organisations;
- ▶ international cooperation on the quality and safety of biological and biotechnological medicinal products;

S. Ruiz (chair)
N. Kruse (vice-chair)



- NIBSC
- EDQM

Veronika Jekerle (Sci. secretariat)
Klara Tiitso (back-up)
Nadja Kriste (secretariat)
Angelo Pacifico (secretariat)

HISTORY

- 1986** **Working Party on Biotechnology and Pharmacy** to advise the CPMP on quality aspects of emerging medicinal products produced by *biotechnological processes*. Develop specific recommendations on quality and safety
- 1995** **Biotechnology Working Party** was established as a permanent working party of the CPMP (now CHMP)
- Now:** 11 meetings / year (2-2,5 days/month)

Early guidelines

- Analysis of the expression construct in cell lines used for production of r-DNA derived proteins (1995)
- Stability testing of biotechnological/biological products (1995)
- Validation of analytical procedures(1996)
- Viral safety evaluation of medicinal products derived from cell lines of human or animal origin (1997)



Mandate

Standing working party to the CHMP

Standing working parties

The current CHMP standing working parties are:

- ▶ Healthcare Professionals' Working Party
- ▶ Biologics Working Party
- ▶ Patients' and Consumers' Working Party
- ▶ Quality Working Party
- ▶ Safety Working Party
- ▶ Scientific Advice Working Party

- maintain and reinforce a uniform approach on biotechnology and biological issues
- avoid/eliminate divergences in assessing biotechnology problems & interpreting biotechnology guidelines
- facilitate the efficient use of European expertise in the scientific review of MAA for biotechnology or biological derived medicinal products (including cell therapy, gene therapy or transgenic expression systems)
- ❖ to provide recommendations to the Committee(s) on all matters relating to **quality aspects** and **safety in relation to quality** of biological and biotechnological MP

Objectives

Support to dossier evaluation: BWP reports with recommendations on quality for approval (Pre-authorisation (100%), Post-authorisation (escalated, <5 %))

80%

Support to scientific advice requests: BWP reports with provision of scientific advice on general and product specific

Guideline preparation, review and update in conjunction with other WPs (and ICH)

Scientific opinions upon request by CHMP on e.g. WHO-related topics, CMDh, Referral or crisis situations (e.g. vaccine shortages, safety issues related to Quality)

20%

Liaison with Interested Parties (Industry associations), European Institutions (EDQM, ECDC, EC, EFSA etc.), other working parties, GMP inspection services etc.

Training and communication

3. Medicinal Products-specific activities

3.1. Pre-Authorisation activities

- Recommendation to CHMP, CAT and SAWP on applications for scientific advice and protocol assistance
- Provision of Scientific Advice for the in-depth review of quality data for similar biological medicinal products upon request of the SAWP
- Recommendation to the CAT on data submitted to the Agency for scientific evaluation and certification of the quality/non-clinical quality data of an ATMP (Art. 18 of Regulation (EC) 1394/2007)
- Contribution to Innovation Task Force
- Contribution to scientific aspects in relation to quality content in similarity assessments for Orphan designation
- Contribution to paediatric investigation plans (PIP) upon request of PDCO



Biologicals and Biotech-derived Product pipeline

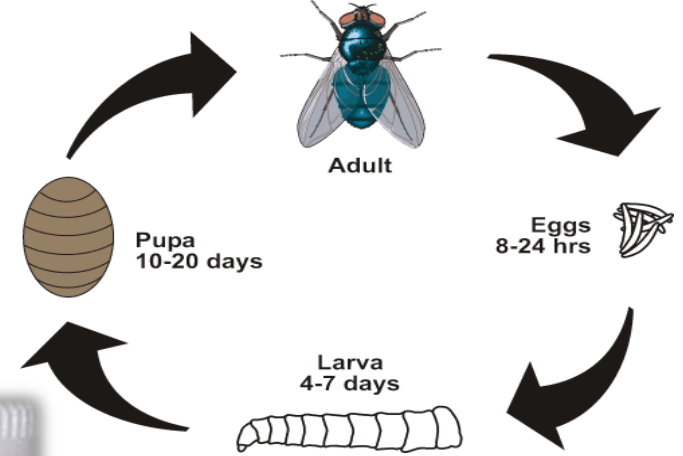
- **Recombinant proteins** (mABs, ABD conjugates, fusion proteins, enzymes etc.)
- TEPs, cell and gene therapies
- Vaccines (Viral, bacterial, other)
- Blood derived products
- Biologically derived products (urine-derived, plant-, tissue- derived)
- Biosimilars of the above (i.e. recombinant)

Mandatory scope - CP

Scientific advice

- ✓ Questions can be put on
 - Quality/biology → Discussion at the BWP and preparation of a report
 - Preclinical
 - Clinical
- ✓ The process is under management and supervision of SAWP
- ✓ CAT (and BWP) provide their input

biologic therapy (larval debridement therapy)



Some examples...

- ✓ Does the Agency agree with the proposed definition of Drug Substance and Drug Product?
- ✓ Quality for an excipient of biological origin
 - Important in selecting, declaring and qualifying the supplier as any change in the quality profile of the excipient may impact the quality of the drug product
 - Regulatory aspects to be considered when using as excipient a plasma-derived medicinal product
 - Dossier to be submitted ?
 - Only batches subjected to official batch release may be used

Some examples...

- ✓ Are the proposed routine control tests relevant?
 - recommended to identify critical tests based on critical quality attributes.
 - proposed IPC and release tests should be based on the final commercial manufacturing process
- ✓ Use of non irradiated bovine serum
- ✓ Viral safety of the various reagents and raw materials used in the process

Some examples...

✓ Comparability issues:

- Change introduced in the manufacturing process between phase II and Phase III clinical trial
- Relevance of the “comparability protocol” : are the characterisation tests satisfactory and suitable to establish the comparability of the pre & post change products

Some examples...

- ✓ Biossay(s), potency assays
 - Need to correlate the acceptance criteria with clinical data
 - Need to establish a strong correlation between phenotypic markers and expected bioactivity (in vitro-in vivo correlation)
 - Demonstrate that potency characteristics remain unchanged in-between testing and administration
 - Investigate the possibility for inclusion of other phenotypic markers
- ✓ Use of “model cells” (from healthy donors) to validate some steps or characteristics when cells from patient are rare and cannot be wasted

Summary

✓ Quality

- Characterisation of the product, quality attributes
- Definition of the process, critical steps,
- Comparability after a change is introduced between CTs
- Selections of the release parameters
 - Case of the final products with a very short shelf life
- Potency assay
- Phenotypic markers
- Cell bank strategy
- Viral safety

✓ Complex products → efficacy/safety profile is also dependent on their quality attributes

3. Medicinal Products-specific activities

3.1. Pre-Authorisation activities

- Recommendation to CHMP, CAT and SAWP on applications for scientific advice and protocol assistance
- Provision of Scientific Advice for the in-depth review of quality data for similar biological medicinal products upon request of the SAWP
- Recommendation to the CAT on data submitted to the Agency for scientific evaluation and certification of the quality/non-clinical quality data of an ATMP (Art. 18 of Regulation (EC) 1394/2007)
- Contribution to Innovation Task Force
- Contribution to scientific aspects in relation to quality content in similarity assessments for Orphan designation
- Contribution to paediatric investigation plans (PIP) upon request of PDCO

Overview

▼ Research and development

Adaptive pathways

▼ Advanced therapies

▼ Advanced therapy development

► Certification procedures for SMEs

Scientific guidelines

Clinical trials

Compassionate use

Compliance

Data on medicines (ISO IDMP standards)

Geriatric medicine

Innovation in medicines

► Home ► Human regulatory ► Research and development ► Advanced therapies ► Advanced therapies ► Certification procedures for SMEs

Certification procedures for micro-, small- and medium-sized enterprises (SMEs)

The European Medicines Agency's Committee for Advanced Therapies (CAT) provides a certification procedure for advanced therapy medicinal products (ATMPs) under development by micro-, small- and medium-sized enterprises (SMEs). This is an opportunity for SMEs to get an assessment of the data they have generated and check that they are on the right track for successful development.

The certification procedure involves the scientific evaluation of quality data and, when available, non-clinical data that SMEs have generated at any stage of the ATMP development process. It aims to identify any potential issues early on, so that these can be addressed prior to the submission of a marketing-authorisation application.

After assessment, the CAT may recommend issuing a certification confirming the extent to which the available data comply with the standards that apply for evaluating a marketing-authorisation application. Following the CAT recommendation, the Agency issues a certification.

The evaluation and certification procedure takes 90 days.

The certification procedure is defined in [Article 18 of Regulation \(EC\) No 1394/2007](#) (the 'ATMP Regulation').

3.2. Evaluation and supervision activities

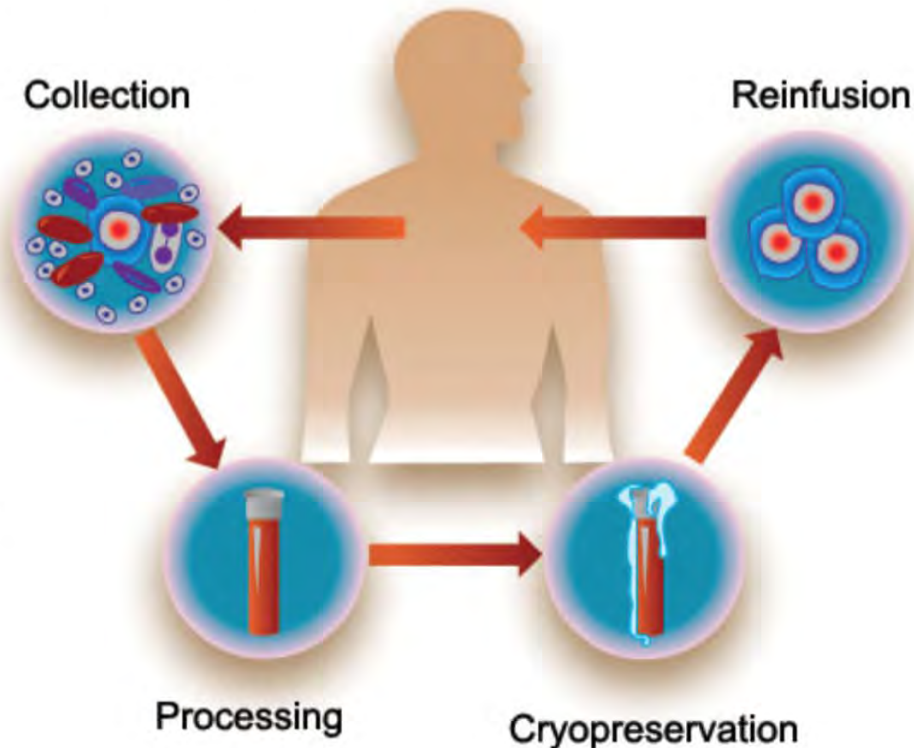
- Recommendation to CHMP and CAT on applications for marketing authorisations and variations
- Recommendation to CHMP on applications for PMF certificates and VAMF certificates
- Recommendation to CHMP on quality in relation to quality and safety aspects of human blood derivatives used as ancillary substances in medical devices and on other ancillary biological substances in medical devices
- Recommendation to CMDh on requests, as adopted by CHMP, affecting scientific aspects in relation to nationally approved medicinal products
- Recommendation to CHMP, as appropriate, on scientific opinion in cooperation with WHO for evaluation of medicinal products intended exclusively for markets outside the community
- Support, as requested, to Inspections activities, quality defects, sampling and testing and liaison with OMCL network and EDQM on activities of mutual interest
- Liaison with and specialised input to CAT, CHMP, QWP, BPWP, BMWP, VWP and GMDP-IWG, PAT team and other groups, working parties and committees, where required, on activities of mutual interest
- Quality support to public health activities related to biological medicinal products

07/2009	CHONDROSELECT	<i>Autologous chondrocytes</i>
07/2012	GLYBERA	<i>AAV-LPL</i>
04/2013	MACI	<i>Matrix-induced autologous chondrocyte implantation</i>
06/2013	PROVENGE	<i>Autologous PBMC activated with PAP-GM-CSF</i>
12/2014	HOLOCLAR	<i>Autologous human corneal epithelial cells</i>
10/2015	IMLYGIC	<i>Oncolytic HSV-1 - GM-CSF</i>
04/2016	STRIMVELIS	<i>Autologous CD34+ - RV hu ADA</i>
06/2016	ZALMOXIS	<i>T cells - HSV-TK</i>
05/2017	SPHEROX	<i>Spheroids of human autologous matrix-associated chondrocytes</i>
12 / 2017	ALOFISEL	<i>Allogeneic expanded adipose stem cells</i>

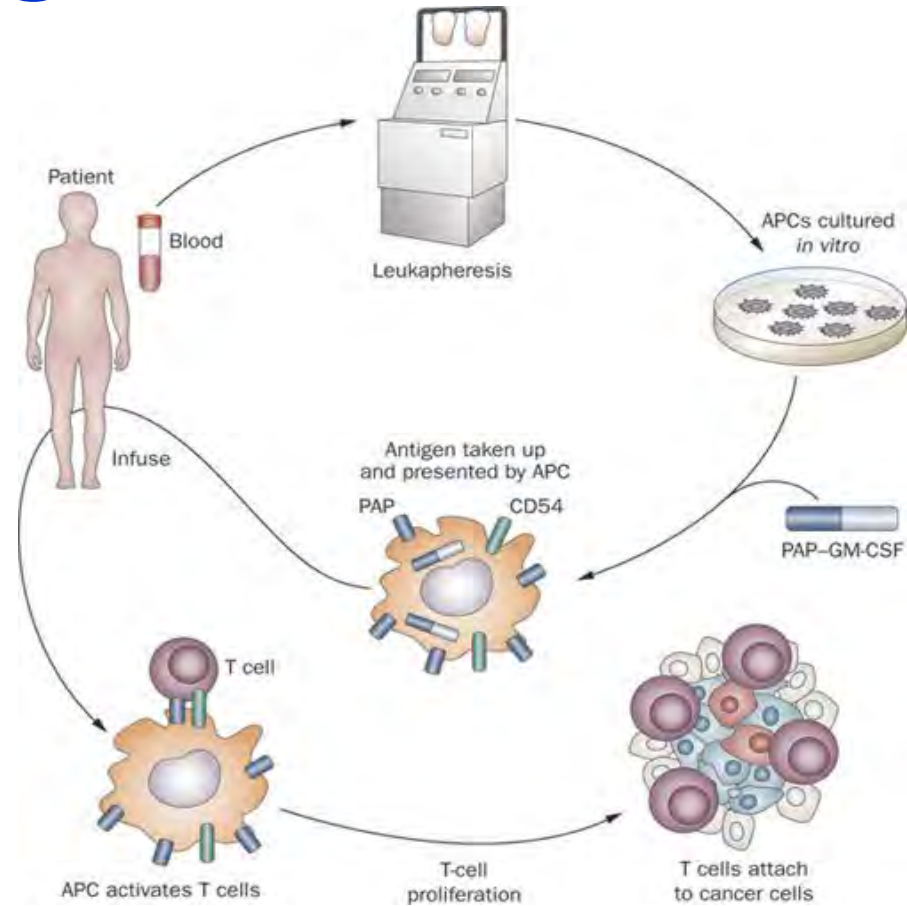
Pharmaceutical complexity ATMPs

- Living cells
- Autologous or patient-specific allogenic
- N=1 batches
- Limited material for testing
- Short in-use shelf life
- Bedside preparation
- Sterility
- *In vivo* GTMP less complex?

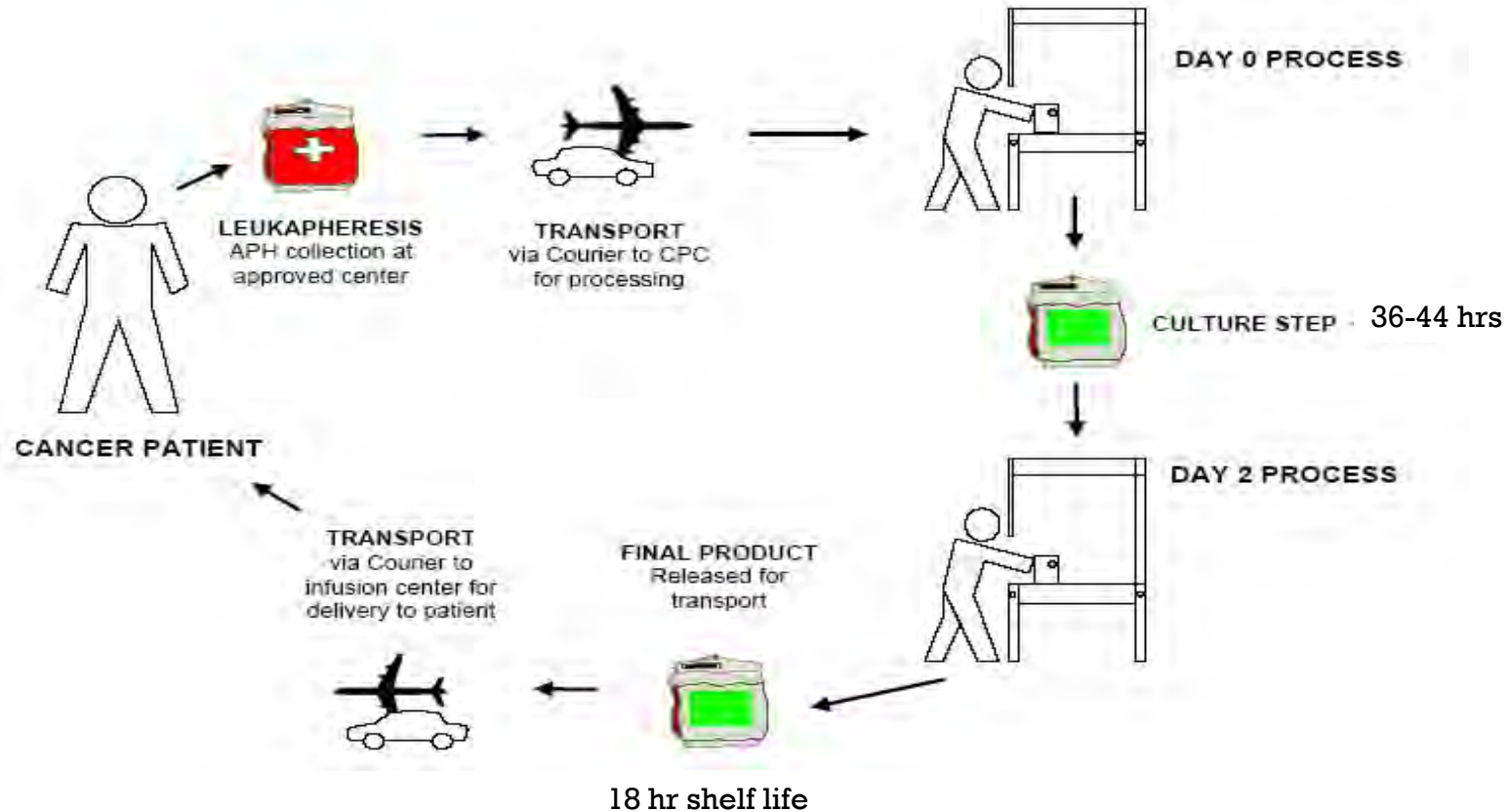
Specific Quality requirements for ATMP (Guidelines)

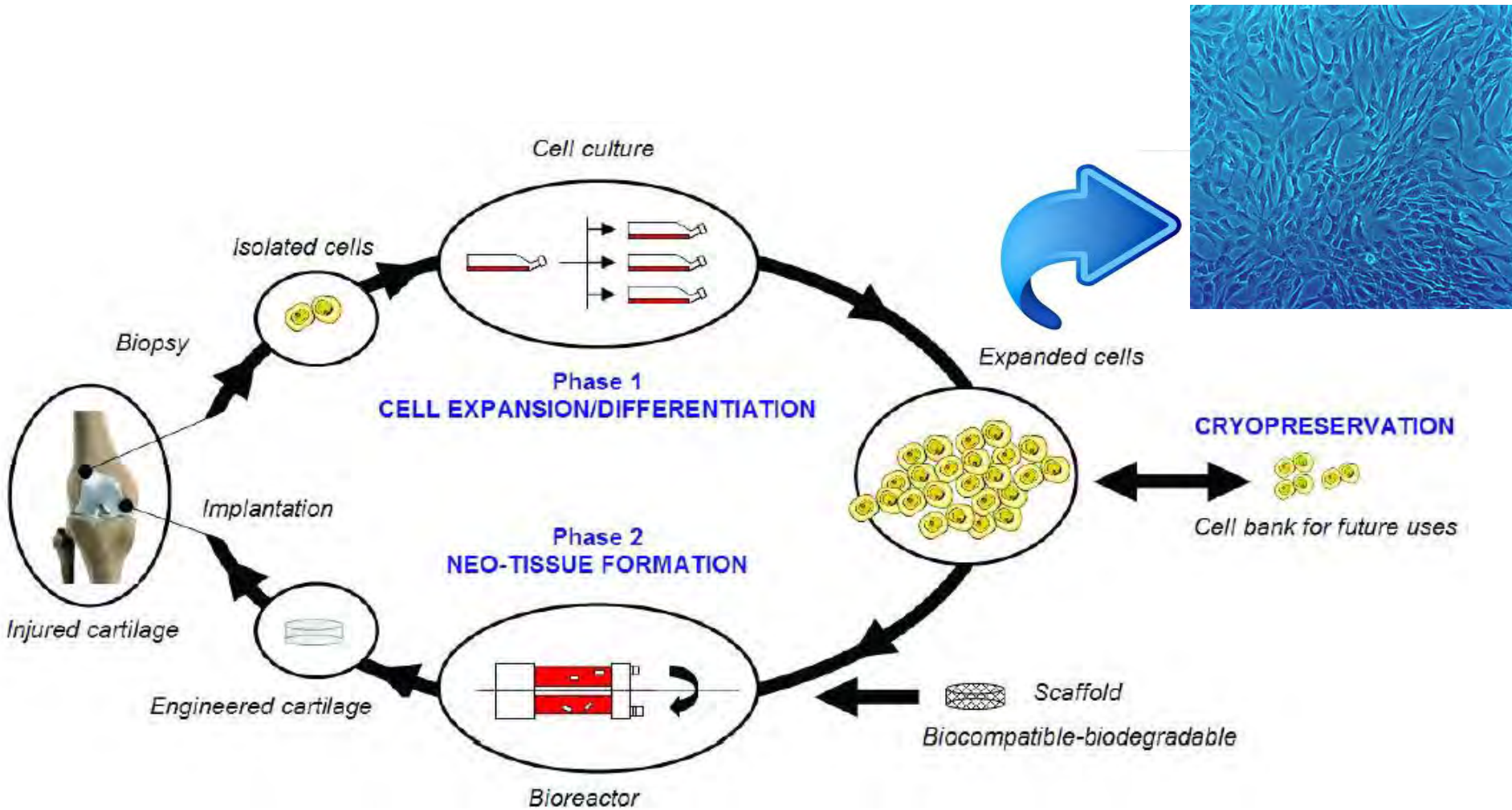


Provenge



Provenge[®] (sipuleucel-T) manufacturing process overview





CHALLENGES VS OTHER BIOLOGICALS

- New type of products
 - Gene therapy
 - Cell therapy
 - Tissue Engineered products
- New challenges in terms of
 - Definition of the product
 - Characterisation and setting specifications
 - Validation and quality control parameters
 - Potency assay
 - Validation of a process

QC control of virus vector DS/DP

Identity	<ul style="list-style-type: none">▪ Physical titer▪ Therapeutic gene expression
Potency	<ul style="list-style-type: none">▪ Infectious titer▪ Particle to infectivity ratio▪ Therapeutic gene expression▪ Biological activity
Purity	<ul style="list-style-type: none">▪ Process-related impurities: Benzonase, Resins, etc.▪ Residual Plasmid DNA (TAT)▪ Residual HC-DNA (SV40 T-Ag, E1A)▪ Residual HCP
Safety	<ul style="list-style-type: none">▪ Sterility, Endotoxin, Mycoplasma▪ Replication-Competent Virus

Aspects of potency testing of virus vector-based GTMPs

- Infection efficiency one aspect of potency but not sufficient
- Expression of therapeutic gene might be considered acceptable for early clinical trials
- At MAA functional assay based on activity of the therapeutic protein and reflecting clinical efficacy should be in place (if feasible)

Characterisation & Target Profile



- **Process development knowledge**
- **Process validation, consistency, comparability, CQA**

Includes

- Identity (defining parameters; e.g. flow cytometry)
- **Viability**
- **Potency**
- Heterogeneity (e.g. level of differentiation)
- Purity (cellular impurities)
- Kariology, tumourigenicity, genetic stability
- **Dose**





Pre-authorisation

Post-opinion

Post-authorisation

Product information

Scientific advice and
protocol assistance

Scientific guidelines

Innovation Task Force

SME office

Paediatric medicine

Geriatric medicine

Orphan designation

[Home](#) [Human regulatory](#) [Scientific guidelines](#) [Biologicals](#)

Biological guidelines

[Email](#) [Print](#) [Help](#) [Share](#)

This section includes the European Medicines Agency's guidelines on **biological medicines**.

The Agency's [Committee for Medicinal Products for Human Use](#) (CHMP) prepares **scientific guidelines** in consultation with regulatory authorities in the European Union (EU) Member States, to help applicants prepare marketing-authorisation applications for human medicines.

Guidelines provide a basis for practical harmonisation of how the EU Member States and the Agency **interpret** and **apply** the detailed requirements for the demonstration of quality, safety and efficacy that are in the **Community directives**.

The Agency strongly encourages applicants and marketing-authorisation holders to follow these guidelines. Applicants need to justify **deviations from guidelines** fully in their applications at the time of submission. The Agency advises applicants to discuss any proposed deviations with EU regulators during medicine development through [scientific advice](#).

Biological guidelines are provided for:

- ▶ [Drug substance](#)
- ▶ [Drug product](#)

- Manufacture, characterisation and control of the DS
- Specifications
- Comparability / biosimilarity
- Plasma-derived medicinal products
- Plasma master file (PMF)
- Vaccines
- Stability



[Pre-authorisation](#)

[Post-opinion](#)

[Post-authorisation](#)

[Product information](#)

[Scientific advice and
protocol assistance](#)

[Scientific guidelines](#)

[Innovation Task Force](#)

[SME office](#)

[Paediatric medicine](#)

[Geriatric medicine](#)

[Orphan designation](#)

▶ [Home](#) ▶ [Human regulatory](#) ▶ [Scientific guidelines](#) ▶ [Biologicals](#)

Biological guidelines

[Email](#) [Print](#) [Help](#) [Share](#)

This section includes the European Medicines Agency's guidelines on **biological medicines**.

The Agency's [Committee for Medicinal Products for Human Use](#) (CHMP) prepares **scientific guidelines** in consultation with regulatory authorities in the European Union (EU) Member States, to help applicants prepare marketing-authorisation applications for human medicines.

Guidelines provide a basis for practical harmonisation of how the EU Member States and the Agency **interpret** and **apply** the detailed requirements for the demonstration of quality, safety and efficacy that are in the **Community directives**.

The Agency strongly encourages applicants and marketing-authorisation holders to follow these guidelines. Applicants need to justify **deviations from guidelines** fully in their applications at the time of submission. The Agency advises applicants to discuss any proposed deviations with EU regulators during medicine development through [scientific advice](#).

Biological guidelines are provided for:

▶ [Drug substance](#)

▶ [Drug product](#)

- Pharmaceutical Development
- Product Information
- Adventitious Agents / Viral Safety
- Transmissible Spongiform Encephalopathies (TSE)
- CJD related
- Investigational Medicinal Products
- GMO

► Home ► Human regulatory ► Research and development ► Scientific guidelines ► Multidisciplinary ►

Multidisciplinary: gene therapy



The European Medicines Agency's scientific guidelines on gene therapy help medicine developers prepare marketing authorisation applications for human medicines.

If you have comments on a document which is open for consultation, use the [form for submission of comments on scientific guidelines](#).

For a complete list of scientific guidelines currently open for consultation, see [Public consultations](#).

Guidelines

- [Safety and efficacy follow-up and risk management of advanced therapy medicinal products](#)
- [Quality, preclinical and clinical aspects of gene therapy medicinal products](#)
- [Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells](#)
- [Development and manufacture of lentiviral vectors](#)
- [Non-clinical studies required before first clinical use of gene therapy medicinal products](#)
- [Non-clinical testing for inadvertent germline transmission of gene transfer vectors](#)
- [Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products](#)

▶ [Home](#) ▶ [Human regulatory](#) ▶ [Research and development](#) ▶ [Scientific guidelines](#) ▶ [Multidisciplinary](#)
▶ [Cell therapy and tissue engineering](#)

Multidisciplinary: cell therapy and tissue engineering

The European Medicines Agency's scientific guidelines on cell therapy and tissue engineering help medicine developers prepare marketing authorisation applications for human medicines.

If you have comments on a document which is open for consultation, use the [form for submission of comments on scientific guidelines](#).



For a complete list of scientific guidelines currently open for consultation, see [Public consultations](#).

Guidelines

- ▶ [Safety and efficacy follow-up and risk management of advanced therapy medicinal products](#)
- ▶ [Human cell-based medicinal products](#)
- ▶ [Potency testing of cell-based immunotherapy medicinal products for the treatment of cancer](#)
- ▶ [Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products](#)
- ▶ [Xenogeneic cell-based medicinal products](#)

OUTPUT FOR 2017

- BWP report Pre-authorisation dossiers: **120** (9 to CAT)
- BWP reports for Scientific Advices: **135** (32 to CAT)
- Plasma Master File – annual updates: **30**
- Plasma Master File – variations: **13**

- ▶ contributing to CHMP scientific opinions in collaboration with the [World Health Organization](#)  (WHO) for the evaluation of [medicines intended for markets outside the European Union](#) (EU);
- ▶ acting as a focus and catalyst for training;
- ▶ contributing to and organising workshops and training sessions on the quality and safety of biological and biotechnological medicinal products;
- ▶ interacting with the [European Directorate for the Quality of Medicines and Healthcare](#)  (EDQM), particularly in relation to European Pharmacopoeia activities, biological standardisation and the activities of the Official Medicines Control Laboratory (OMCL) network;
- ▶ preparing statements on general or product-specific matters for the public;
- ▶ on request of the CHMP, constituting a rapid-acting crisis group to take on specific issues relating to the quality of biological or biotechnological medicinal products, including quality in relationship to safety aspects, with the objective of exchanging information on a European level and co-ordinating responses to the public in a timely manner.

PCV-1

in

Rotarix

Viral Nucleic Acids in Live-Attenuated Vaccines: Detection of Minority Variants and an Adventitious Virus^{▽†}

Joseph G. Victoria,^{1,2} Chunlin Wang,³ Morris S. Jones,⁴ Crystal Jaing,⁵ Kevin McLoughlin,⁵ Shea Gardner,⁵ and Eric L. Delwart^{1,2*}

Blood Systems Research Institute, San Francisco, California 94118¹; Dept. of Laboratory Medicine, University of California, San Francisco, California 94118²; Stanford Genome Technology Center, Stanford, California 94304³; Clinical Investigation Facility, David Grant USAF Medical Center, Travis AFB, California 94535⁴; and Lawrence Livermore National Laboratory, Livermore, California 94551⁵

Received 22 December 2009/Accepted 25 March 2010

Metagenomics and a panmicrobial microarray were used to examine eight live-attenuated viral vaccines. Viral nucleic acids in trivalent oral poliovirus (OPV), rubella, measles, yellow fever, varicella-zoster, multivalent measles/mumps/rubella, and two rotavirus live vaccines were partially purified, randomly amplified, and pyrosequenced. Over half a million sequence reads were generated covering from 20 to 99% of the attenuated viral genomes at depths reaching up to 8,000 reads per nucleotides. Mutations and minority variants, relative to vaccine strains, not known to affect attenuation were detected in OPV, mumps virus, and varicella-zoster virus. The anticipated detection of endogenous retroviral sequences from the producer avian and primate cells was confirmed. Avian leukosis virus (ALV), previously shown to be noninfectious for humans, was present as RNA in viral particles, while simian retrovirus (SRV) was present as genetically defective DNA. Rotarix, an orally administered rotavirus vaccine, contained porcine circovirus-1 (PCV1), a highly prevalent nonpathogenic pig virus, which has not been shown to be infectious in humans. Hybridization of vaccine nucleic acids to a panmicrobial microarray confirmed the presence of endogenous retroviral and PCV1 nucleic acids. Deep sequencing and microarrays can therefore detect attenuated virus sequence changes, minority variants, and adventitious viruses and help maintain the current safety record of live-attenuated viral vaccines.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 February 2014
EMA/CHMP/BWP/814397/2011
Committee for Medicinal Products for Human use (CHMP)

Guideline on the use of porcine trypsin used in the manufacture of human biological medicinal products

Draft Agreed by Biologicals Working Party	December 2012
Adoption by CHMP for release for consultation	21 February 2013
Start of public consultation	1 March 2013
End of consultation (deadline for comments)	31 August 2013
Agreed by Biologicals Working Party	15 January 2014
Adoption by CHMP	20 February 2014
Date for coming into effect	1 September 2014

Keywords

Porcine trypsin, adventitious agents, virus

scope



Trypsin purified from porcine pancreatic glands for use as a reagent in the manufacture of human medicinal products:

- as a reagent for cell culture (vaccines, ATMP...)
- to activate virus particles
- as a protein processing reagent.

195 11. Risk Assessment

196 This Guideline provides a general quality specification for porcine trypsin, especially with respect to
197 viral safety, and various measures that should be applied during the production of porcine trypsin to
198 minimize the viral risk are described. No combination of the measures outlined below can guarantee
199 complete viral safety, but rather they reduce the risk involved in the use of trypsin in the manufacture
200 of medicinal products. It is therefore necessary for the manufacturer of a medicinal product to take
201 account of this when choosing the trypsin for a particular use by making a risk assessment. The risk
202 assessment should follow the general principles outlined in Ph. Eur. 5.1.7 Viral Safety. Such risk
203 analysis should consider (1) the epidemiology and control of the animals from which the starting
204 material is sourced, (2) the availability of suitable virus test methods and the stage at which such
205 testing is implemented, (3) virus inactivation by trypsin itself, (4) the virus inactivation/removal during
206 manufacture of the trypsin, (5) the stage of manufacture of the medicinal product at which trypsin is
207 used as a reagent, (6) the risk of virus replication in cell cultures used for production of the medicinal
208 product, (7) additional virus inactivation/removal steps applied during the manufacture of the
209 medicinal product, (8) the amount of trypsin to produce a dose of medicinal product, and (9) the route
210 of administration of the medicinal product.

211 12. Regulatory Aspects

212 The Marketing Authorisation Holder/Applicant of the medicinal product should have sufficient
213 information on the trypsin to allow a comprehensive risk assessment and provide a sufficient data
214 package to the competent authority for assessment. This should include a description of testing
215 methods and the stage at which virus testing is performed, as well as the volumes and sensitivity of
216 the virus tests. Study reports validating virus reduction steps should be provided according to
217 Guideline CHMP/BWP/268/95.

218 This guideline is for prospective implementation. Nevertheless in light of the reported contamination
219 events, it is recommended to re-assess virus safety of authorized live virus vaccines that use porcine
220 trypsin in the manufacturing process.

6. Contribution to dialogue and engagement with stakeholders and external parties

6.1. Workshops

Workshop with stakeholders on quality aspects in accelerated access approaches (i.e. PRIME) (timeline Q3/Q4 2018)

6.2. Other activities with stakeholders and external parties

Meeting with Interested Parties (EFPIA, Vaccines Europe, PPTA, IPFA, EuropaBio, EBE, Medicines for Europe, APIC and other interested parties) on issues of joint interest. To be organised in the margins of one of the BWP plenary meetings

Emerging pathogens

Workshop on viral safety of plasma-derived medicinal products with respect to hepatitis E virus

Details

Documents

Multimedia

Title Workshop on viral safety of plasma-derived medicinal products with respect to hepatitis E virus

Date 28/10/2014 - 29/10/2014

Location European Medicines Agency, London, UK

Summary The purpose of this workshop is to obtain further information on the safety of plasma-derived medicinal products with respect to the hepatitis E virus (HEV). It will provide the basis for deciding what further action may be needed, including the possible update of the current guidance on plasma-derived medicinal products and/or development of a [reflection paper](#) specifically on viral safety of plasma derived medicinal products with respect to HEV. Registration by invitation only. Registration open until 30 September 2014.

News and press releases

► **Events**

What's new

Committee highlights

Therapeutic areas:
latest updates

Medicine evaluation
figures

Publications





Press and social media

Open consultations

RSS feeds

► Home ► News and Events ► Events

Joint Biologics Working Party / Quality Working Party workshop with stakeholders in relation to prior knowledge and its use in regulatory applications

 Email  Print  Help  Share

Details

Documents

Multimedia

Title Joint Biologics Working Party / Quality Working Party workshop with stakeholders in relation to prior knowledge and its use in regulatory applications


Date 23/11/2017 - 23/11/2017

Location European Medicines Agency, London, UK

Summary The term 'prior knowledge' can refer to both a company's proprietary knowledge of formulation and manufacturing development of medicinal products and external knowledge from published scientific literature. The use of such prior knowledge to support the development of product formulations, manufacturing processes and control strategies, could be justifiable in certain circumstances. Through a combination of presentations, industry case studies and panel discussions, this joint workshop with regulators and the pharmaceutical industry aims to reach an agreed understanding on what is (and isn't) considered to be prior knowledge, how can such prior knowledge be used in regulatory submissions, how to justify its use and how to present it in the dossier. EMA will publish a report with conclusions from the workshop. It may also consider further follow-up guidance.

Live broadcast

► 23 November 2017
9:00 - 17:00 UK time

 To watch the broadcast click on 'Multimedia' tab.

Registration

► Registration by invitation only

Video recording

A video recording will be made available after the event

Contact point:

bwpsecretariat@ema.europa.eu

4. Input in European activities

4.1. Training for the network and knowledge building

- Assessor training on overview guidance as part of the CHMP assessment report in relation quality information (Q2 2018)
- Maintain awareness of issues arising in order to identify the need for review and update of Guidelines and development of additional guidance documents

4.2. Support to and cooperation with EU institutions and Network

- With EDQM: Scientific input for the elaboration and revision of European Pharmacopoeia monographs and scientific input and collaboration with EDQM including bilateral meetings, ad hoc discussion at BWP, Group 6/6B/15 contribution and participation to the BSP Steering Committee meetings
- Organise an annual meeting with relevant experts on Influenza vaccines: for strain selection and to elaborate a proposal for the strain composition of the influenza vaccine for the forthcoming annual vaccination campaign. Other involved parties: VWP, CMDh, WHO
- With the network and stakeholders: Scientific input to quality aspects for biological medicinal products under accelerated access schemes (Adaptive pathways and PRIME) and support to cross-Agency project in relation to specific activities and knowledge sharing

BWP workplan 2018

New guidelines:

- Structure and properties for the determination of new active substance (NAS) status of biological substances
- Q&A on Haemagglutination Inhibition (HI) test for qualification of seasonal influenza vaccine (inactivated) seed preparations
- Position Statement on CJD and plasma-derived and urine-derived medicinal products
- Public statement on bovine-spongiform-encephalopathy risk of materials of bovine origin during manufacture of vaccines
- Pharmaceutical Aspects of the Product Information for Human Vaccines
- Scientific data requirements for a PMF

Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (CHMP/GTWP/671639/2008)

Leading group CAT

Target date Preparation of first draft of revised guideline for public consultation by Q2 2018

Comments Contribution to preparation of first revised draft

BWP WORKPLAN 2018



Workshops, stakeholder & expert meetings:

- ✓ Stakeholder workshop on accelerated access and quality
- ✓ Training on overview guidance for D80 Overview CHMP/CAT AR
- ✓ Interested Parties meeting
- ✓ Annual strain selection meeting (Seasonal Influenza)

Launch of adaptive pathways pilot project

EMA launched the adaptive pathways pilot project in March 2014.

The concept of adaptive pathways foresees an early approval of a medicine for a restricted patient population based on small initial clinical studies. The first approval is followed by progressive adaptations of the marketing authorisation to expand access to the medicine to broader patient populations based on data gathered from its real world use and additional studies.

"The adaptive pathways approach seeks to maximize the positive impact of new medicines on public health by balancing timely access for patients with the need to provide adequate evolving information on their benefits and risks,"

Hans-Georg Eichler, EMA Senior Medical Officer

Adaptive pathways is particularly relevant for medicines with the potential to treat serious conditions with an unmet medical need, and may reduce the time to a medicine's approval or to its reimbursement for targeted patient groups.

PRIME: priority medicines



PRIME is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier.

Through PRIME, the Agency offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicines applications.

This will help patients to benefit as early as possible from therapies that may significantly improve their quality of life.

Accelerated assessment

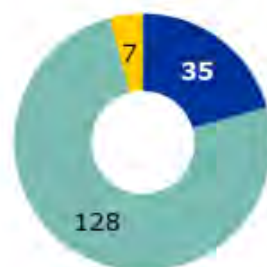
PRIME builds on the existing regulatory framework and tools already available such as [scientific advice](#) and [accelerated assessment](#). This means that developers of a medicine that benefitted from PRIME can expect to be eligible for [accelerated assessment](#) at the time of application for a [marketing authorisation](#).

Fostering early dialogue

By engaging with medicine developers early on, PRIME is aimed at improving [clinical trial](#) designs so that the data generated is suitable for evaluating a [marketing-authorisation](#) application.

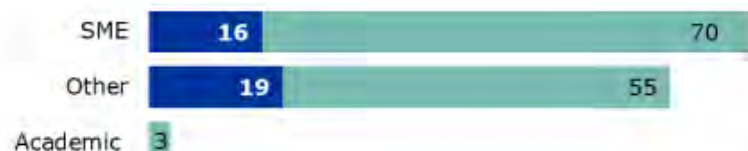
Early dialogue and [scientific advice](#) also ensure that patients only participate in trials designed to provide the data necessary for an application, making the best use of limited resources.

Cumulative overview of recommendations on PRIME eligibility requests adopted by 22 February 2018



■ Granted ■ Denied ■ Out of scope*

By type of applicant



■ Granted ■ Denied

By therapeutic area



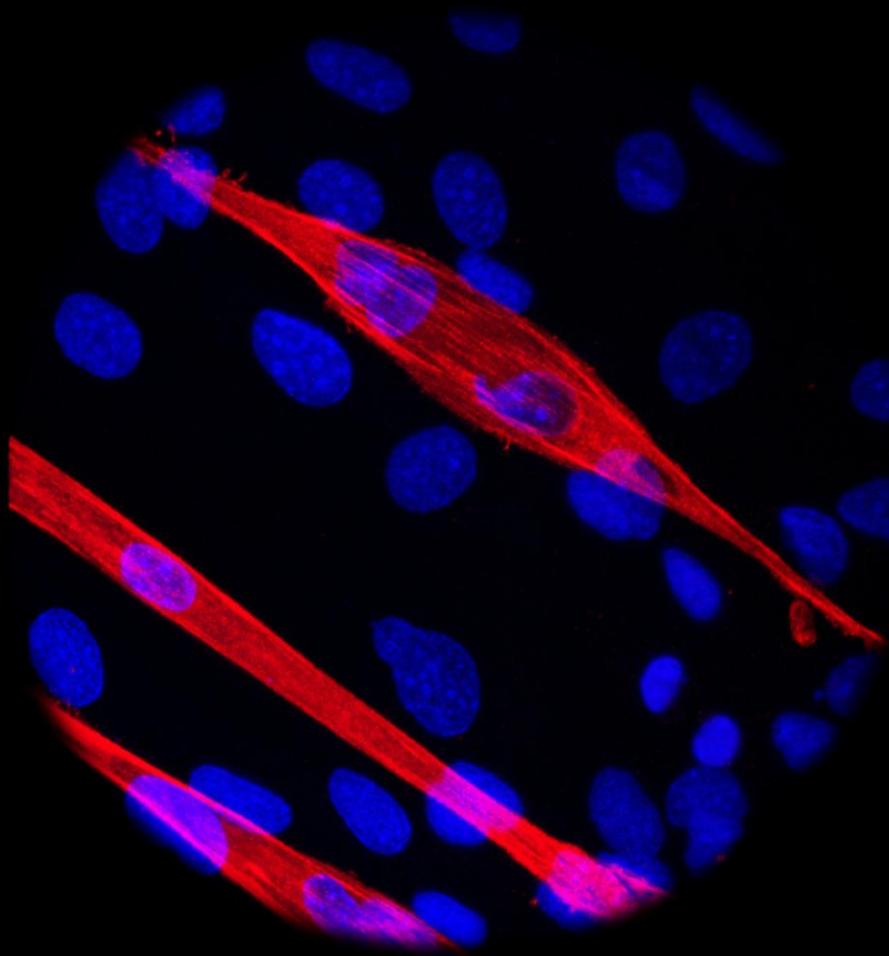
* This indicates eligibility requests received but not started by EMA as they were deemed outside the scope of the scheme or with a format and content inadequate to support their review. These are not included in the breakdown by type of applicant or by therapeutic area.

Table 3. PRIME Products

Proprietary Name	Description	Therapeutic Area	Therapeutic Indication	Developer
SPK-9001	adeno-associated viral vector containing factor IX gene variant	hematology	treatment of haemophilia B	Spark Therapeutics
BMN 270	adeno-associated viral vector serotype 5 containing a B-domain deleted variant of human coagulation factor VIII gene	hematology	treatment of haemophilia A	BioMarin
AMT-060	adeno-associated viral vector serotype 5 containing human factor IX gene	hematology	treatment of haemophilia B	uniQure
AVXS-101	Adeno-associated viral vector serotype 9 containing the human SMN gene	neurology	treatment of pediatric patients diagnosed with spinal muscular atrophy type 1	AveXis
DNX-2401	adenovirus serotype 5 containing partial E1A deletion and an integrin-binding domain	oncology	treatment of recurrent glioblastoma in patients for which a gross total resection is not possible or advisable or who refuse further surgery	DNAtrix Therapeutics
ATA129	allogeneic Epstein-Barr virus-specific cytotoxic T lymphocytes	hematology	treatment of patients with Epstein-Barr virus-associated post-transplant lymphoproliferative disorder in the allogeneic hematopoietic cell transplant setting refractory to rituximab	Atara Biotherapeutics
Lentiglobin	autologous CD34+ hematopoietic stem cells transduced with lentiviral vector encoding the human β^{A-T87Q} -globin gene	hematology	treatment of beta-thalassaemia major	Bluebird Bio
NY-ESO-1c259T	autologous CD4 and CD8 T cells transduced with lentiviral vector containing an affinity-enhanced T cell receptor to target the cancer-testis tumor antigen	oncology	treatment of HLA-A*0201, HLA-A*0205, or HLA-A*0206 allele-positive patients with inoperable or metastatic synovial sarcoma who have received prior chemotherapy and whose tumor expresses the NY-ESO-1 tumor antigen	Adaptimmune
JCAR017	autologous CD4 ⁺ and CD8 ⁺ T cells expressing a CD19-specific chimeric antigen receptor	oncology	treatment of relapsed/refractory diffuse large B cell lymphoma (DLBCL)	Juno Therapeutics
CTL019	autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19	oncology	treatment of pediatric patients with relapsed or refractory B cell acute lymphoblastic leukemia	Novartis

- **Biologics – challenging field including new concepts & approaches**
- **Open mind required (adapt and reconsider established criteria, if necessary)**
- **Develop (and maintain) the spirit of experience- and competence-sharing**
- **Propose sound and scientifically-based advice and recommendations**

*Thank
You!*



sruiz@aemps.es