MINISTERIO DE SANIDAD Y POLÍTICA SOCIAL

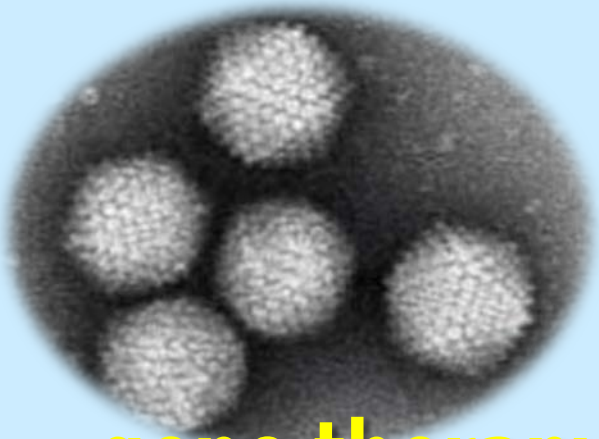
agencia española de medicamentos y productos sanitarios

Barcelona - 05/03/2018

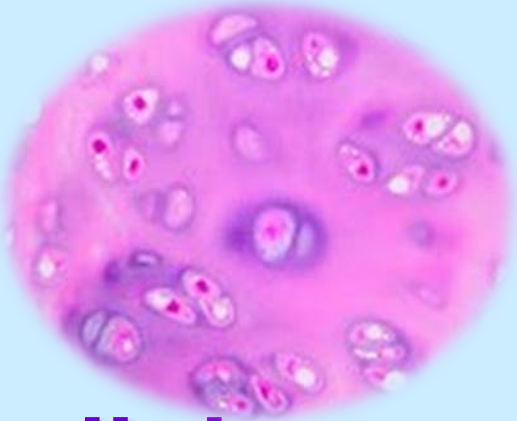
advanced therapies in the EU

Sol Ruiz - AEMPS

ATMP in the EU



gene therapy



cell therapy

tissue engineering

REGLAMENTO (CE) Nº 1394/2007 DEL PARLAMENTO EUROPEO Y DEL CONSEJO

de 13 de noviembre de 2007

sobre medicamentos de terapia avanzada y por el que se modifican la Directiva 2001/83/CE y el Reglamento (CE) nº 726/2004

(Texto pertinente a efectos del EEE)

Artículo 1

Objeto

El presente Reglamento establece normas específicas para la autorización, la supervisión y la farmacovigilancia de los medicamentos de terapia avanzada.

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.

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.

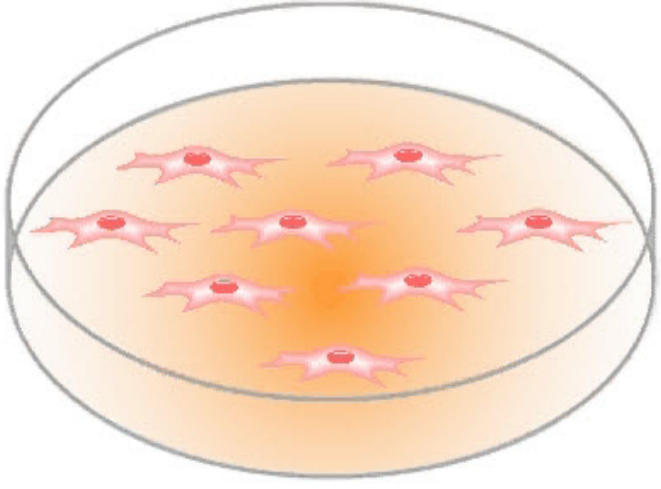
For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

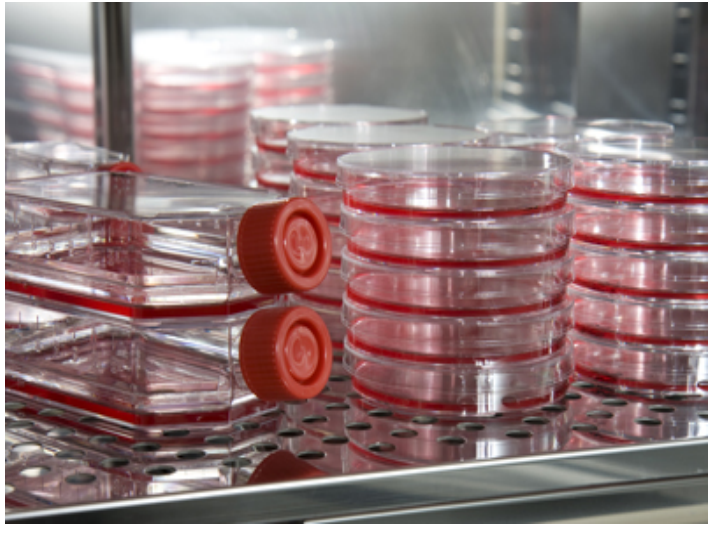
Regulation (EC) No 1394/2007

Tissue engineered product means a product that:

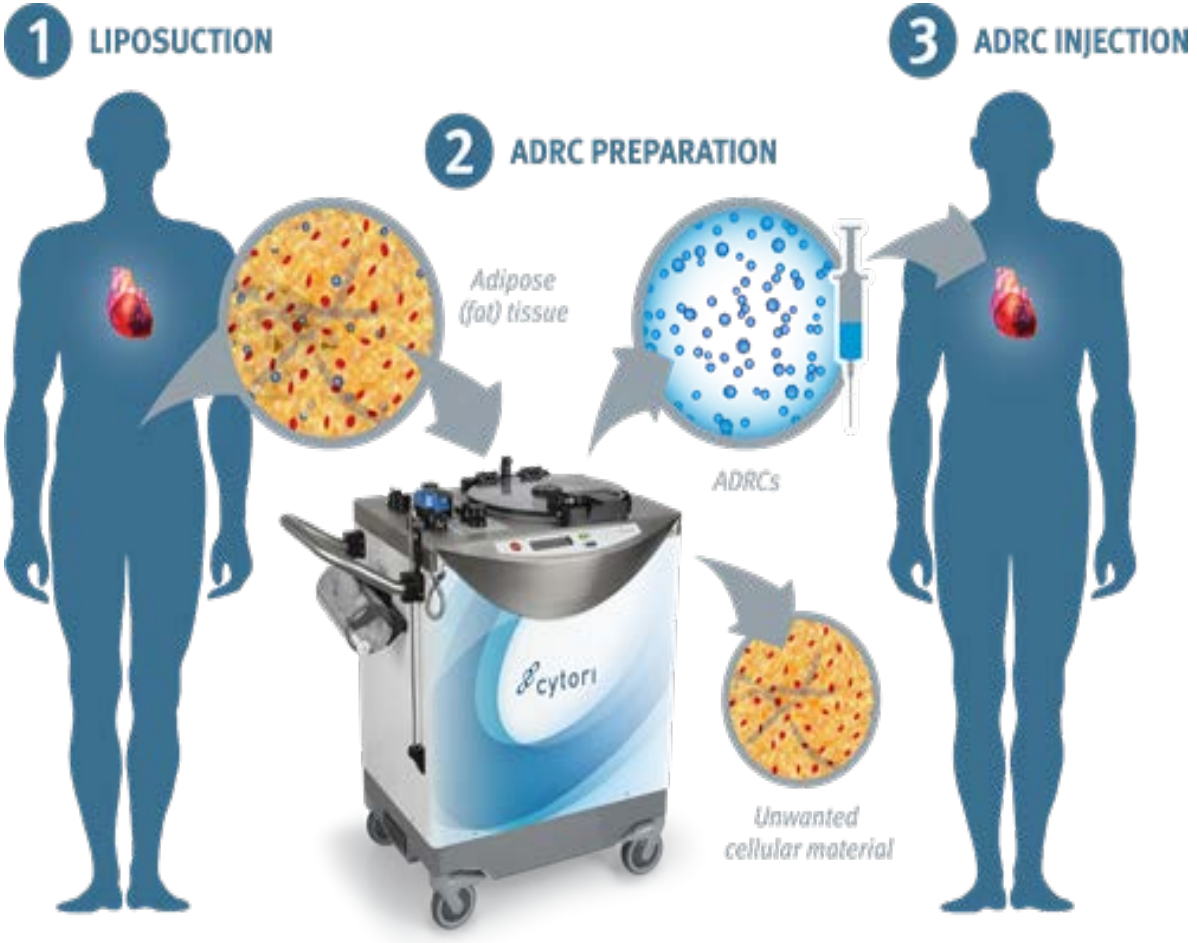
— contains or consists of engineered cells or tissues, and

— 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
Adipose (fat) tissue
ADRCs
cytori
Unwanted cellular material

atmp

medicamento de terapia avanzada

DEBE CUMPLIR LA LEGISLACIÓN DE MEDICAMENTOS

- autorización de uso: comercialización, investigación clínica, uso compasivo
- garantías de calidad, seguridad, eficacia
- son aplicables **GMP** (producción y control), **GLP** (estudios no clínicos) y **GCP** (ensayos clínicos)

aemps

- investigación clínica, uso compasivo
- autorización por *cláusula de exclusión*

ema

autorización de comercialización en la UE

SCOPE

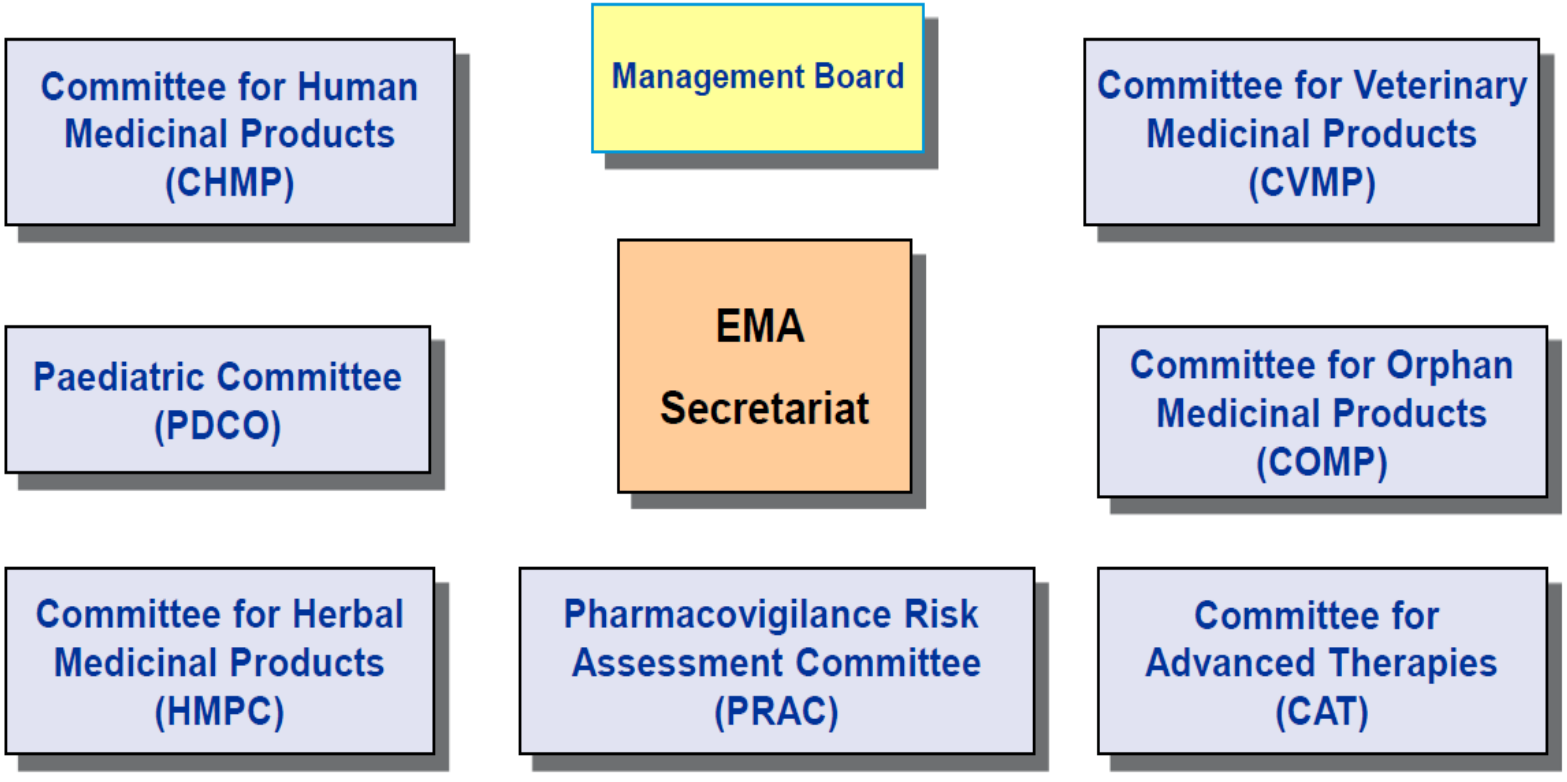
Advanced therapy medicinal products which are intended to be placed on the market in Member States and either **prepared industrially** or manufactured by a method involving an **industrial process** (Title II of Directive 2001/83).

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**

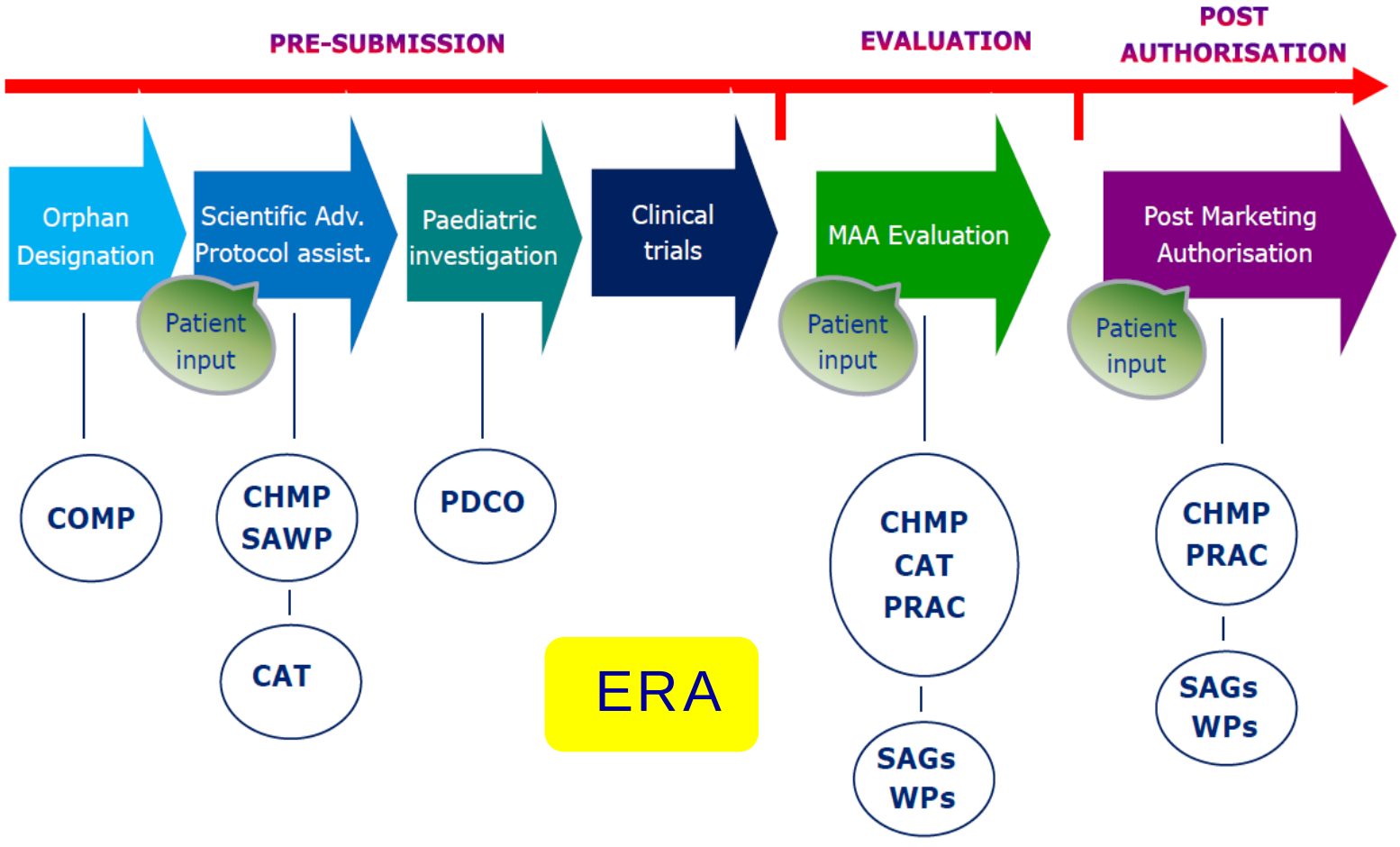
european medicines agency

CENTRALIZED PROCEDURE

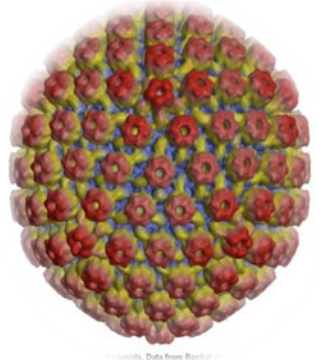

Committee for Human Medicinal Products (CHMP)
Management Board
Committee for Veterinary Medicinal Products (CVMP)
Paediatric Committee (PDCO)
EMA Secretariat
Committee for Orphan Medicinal Products (COMP)
Committee for Herbal Medicinal Products (HMPC)
Pharmacovigilance Risk Assessment Committee (PRAC)
Committee for Advanced Therapies (CAT)

from EMA

Centralised procedure - product life-cycle



from EMA



maa

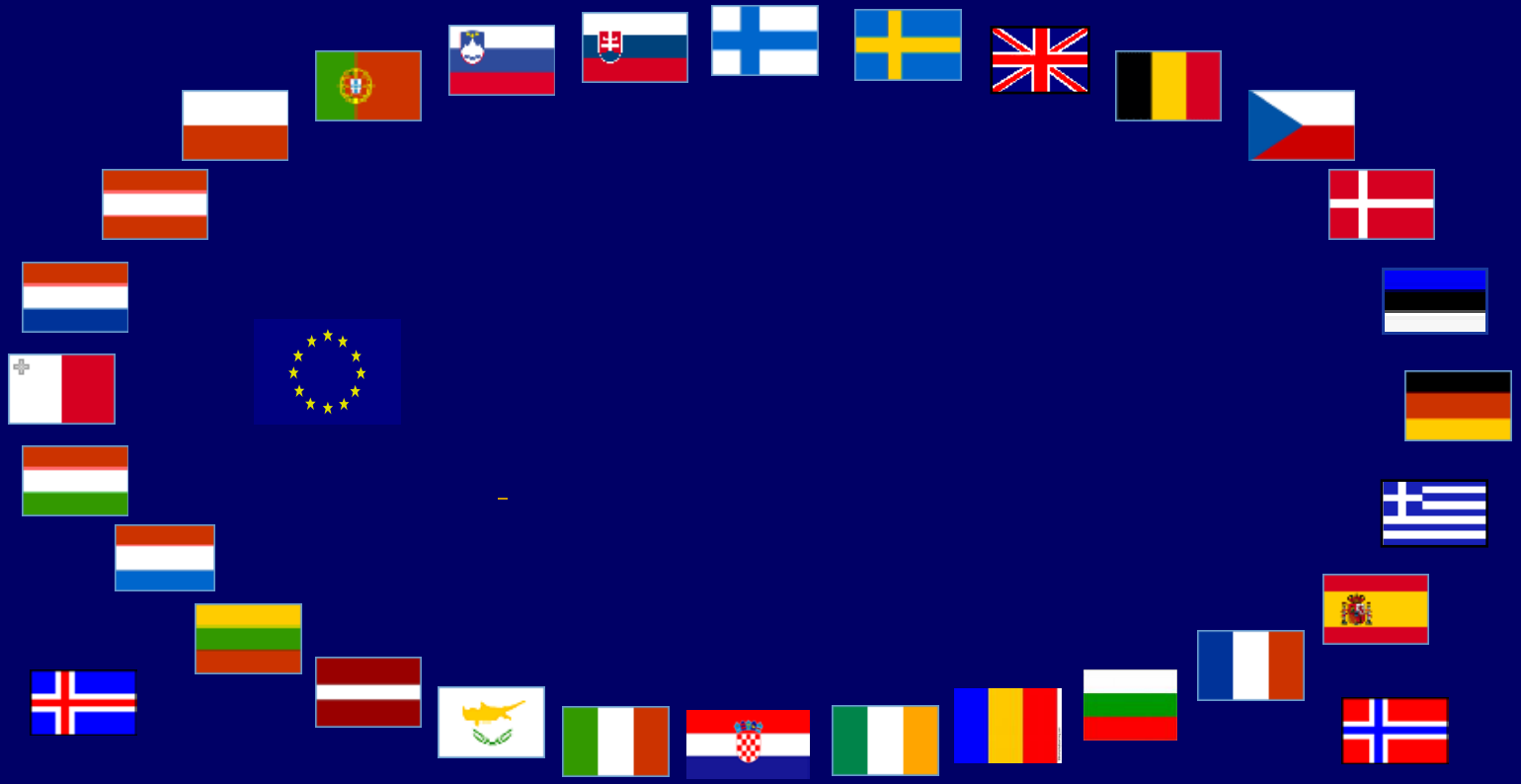
bWp QUALITY

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>.


TOYO TIRES
TOYO TIRES
BIRMINGHAM

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

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

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.eu
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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***

La terapia génica alcanza por fin al futuro

EE UU aprobará en septiembre la primera terapia génica para uso comercial. Servirá para tratar a enfermos de leucemia con mal pronóstico

DANIEL MEDIAVILLA

26 JUL 2017 - 20:10 CEST

La primera terapia génica para uso comercial será por fin una realidad en septiembre. EE UU tiene previsto aprobar para entonces el primer tratamiento. Fabricado por la farmacéutica Novartis, ha mostrado su efectividad en enfermos de leucemia con muy mal pronóstico. En un ensayo en 12 países, el 83% vieron como la enfermedad remitía. Un año después, dos tercios seguían libres de cáncer.

El funcionamiento de la terapia consiste en extraer los propios linfocitos del paciente, llevarlos a un laboratorio de la compañía farmacéutica, modificarlos genéticamente para que sean capaces de atacar a las células de cáncer y volver a inyectárselos al enfermo. Eso se logra empleando virus del sida mutilados que utilizan la capacidad de este microorganismo para secuestrar las células humanas y ponerlas a su servicio. En este caso, el potencial del VIH para el mal se aprovecha para mejorar las células del sistema inmune que suele destruir.

Este tipo de glóbulos blancos mejorados han provocado efectos secundarios graves en el pasado. La muerte de cinco pacientes por inflamación del cerebro obligó a la empresa Juno Therapeutics, en EE UU, a detener un ensayo que utilizaba una técnica similar. Por el momento, Novartis no ha observado este tipo de problemas en sus ensayos.

FDA News Release

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

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 News Release

FDA approval brings first gene therapy to the United States

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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.

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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.

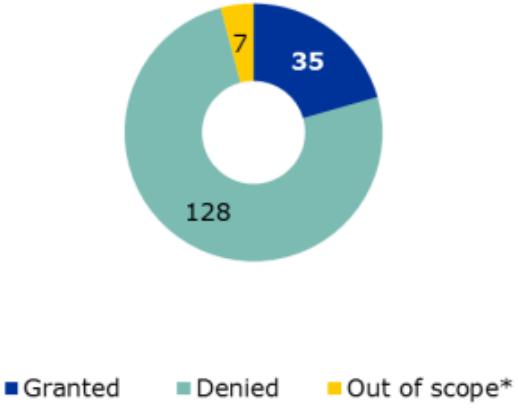
Fostering early dialogue

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.

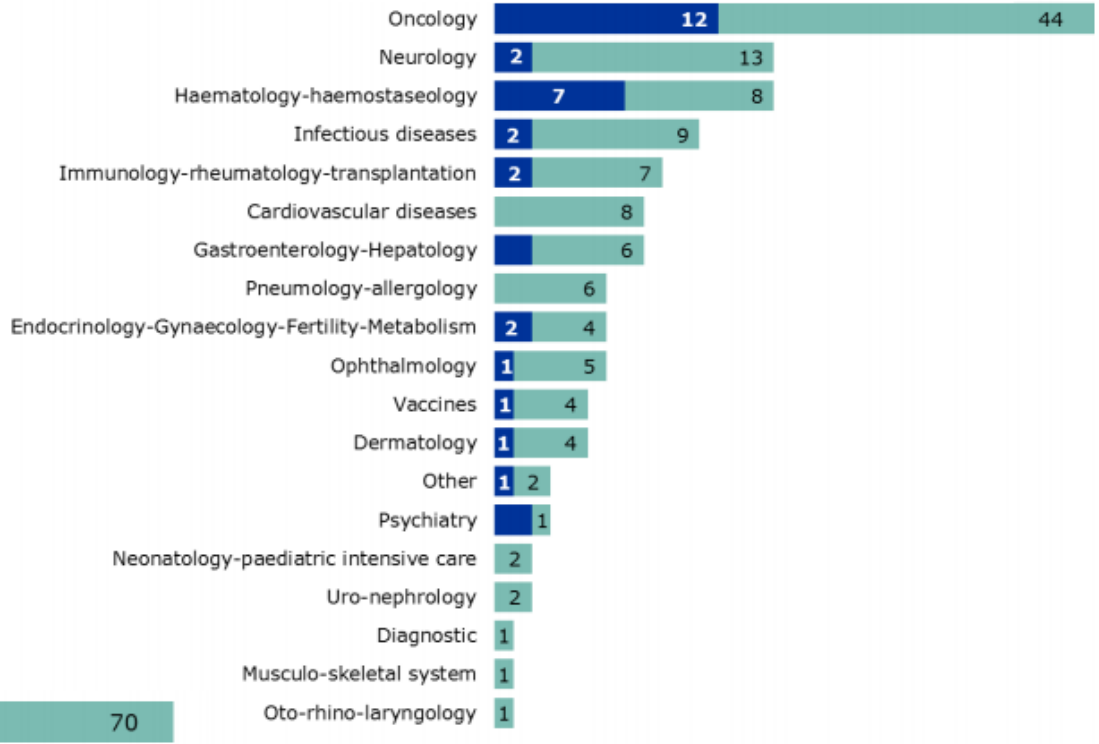
Early dialogue and scientific advice also ensure that patients only participate in trials designed to provide the data necessary for an application, making the best use of limited resources.

EMA Annual Report 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2015/04/WC500186306.pdf (accessed October 2016)
EMA. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac058096f643 (accessed October 2016)

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



By therapeutic area



By type of applicant

*** 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 $\beta^{A\text{-}T87Q}$-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

SCOPE

(6) This Regulation is a *lex specialis*, which introduces additional provisions to those laid down in Directive 2001/83/EC. The scope of this Regulation should be to regulate 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, in accordance with the general scope of the Community pharmaceutical legislation laid down in Title II of Directive 2001/83/EC. Advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Regulation whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined.

I. DISPOSICIONES GENERALES

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

6277 *Real Decreto 477/2014, de 13 de junio, por el que se regula la autorización de medicamentos de terapia avanzada de fabricación no industrial.*

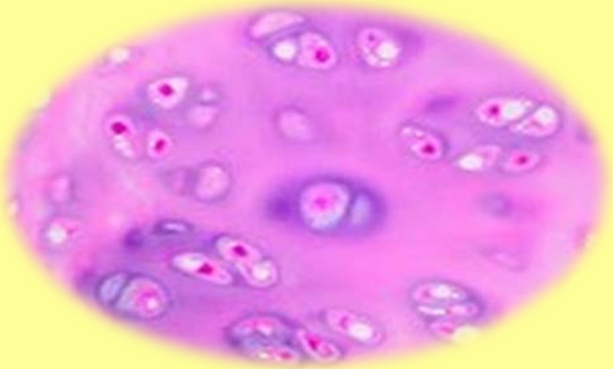
El Reglamento (CE) n.º 1394/2007 del Parlamento Europeo y del Consejo, de 13 de noviembre de 2007, sobre medicamentos de terapia avanzada y por el que se modifican la Directiva 2001/83/CE y el Reglamento (CE) n.º 726/2004, define como «medicamento de terapia avanzada» a los medicamentos de terapia génica, los medicamentos de terapia celular somática, los productos de ingeniería tisular y los medicamentos combinados de terapia avanzada.

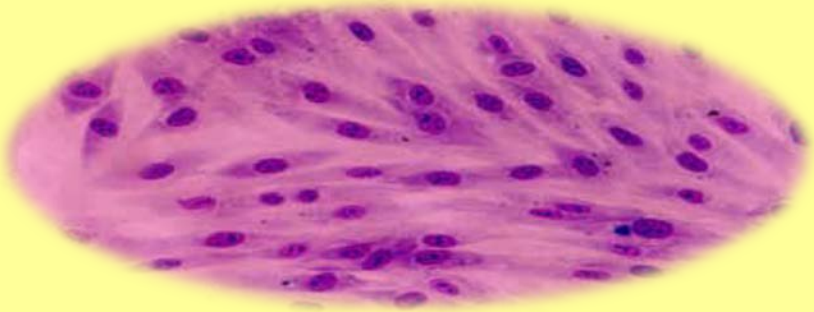
Por su parte, la Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios, por la que se incorporan al ordenamiento jurídico nacional las disposiciones de la Directiva 2001/83/CE del Parlamento Europeo y del Consejo, de 6 de noviembre de 2001, por la que se establece un código comunitario sobre medicamentos para uso humano, define «medicamento de uso humano» como: «toda sustancia o combinación de sustancias que se presente como poseedora de propiedades para el tratamiento o prevención de enfermedades en seres humanos o que pueda usarse en seres humanos o administrarse a seres humanos con el fin de restaurar, corregir o modificar las funciones fisiológicas ejerciendo una acción farmacológica, inmunológica o metabólica, o de establecer un diagnóstico médico».

Al igual que sucede con otros medicamentos tales como las fórmulas magistrales o

“established therapies”

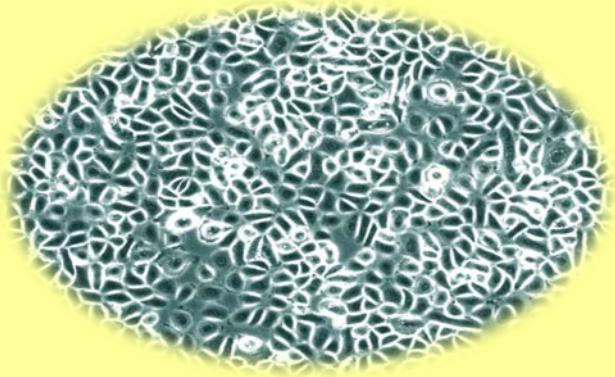
chondrocytes

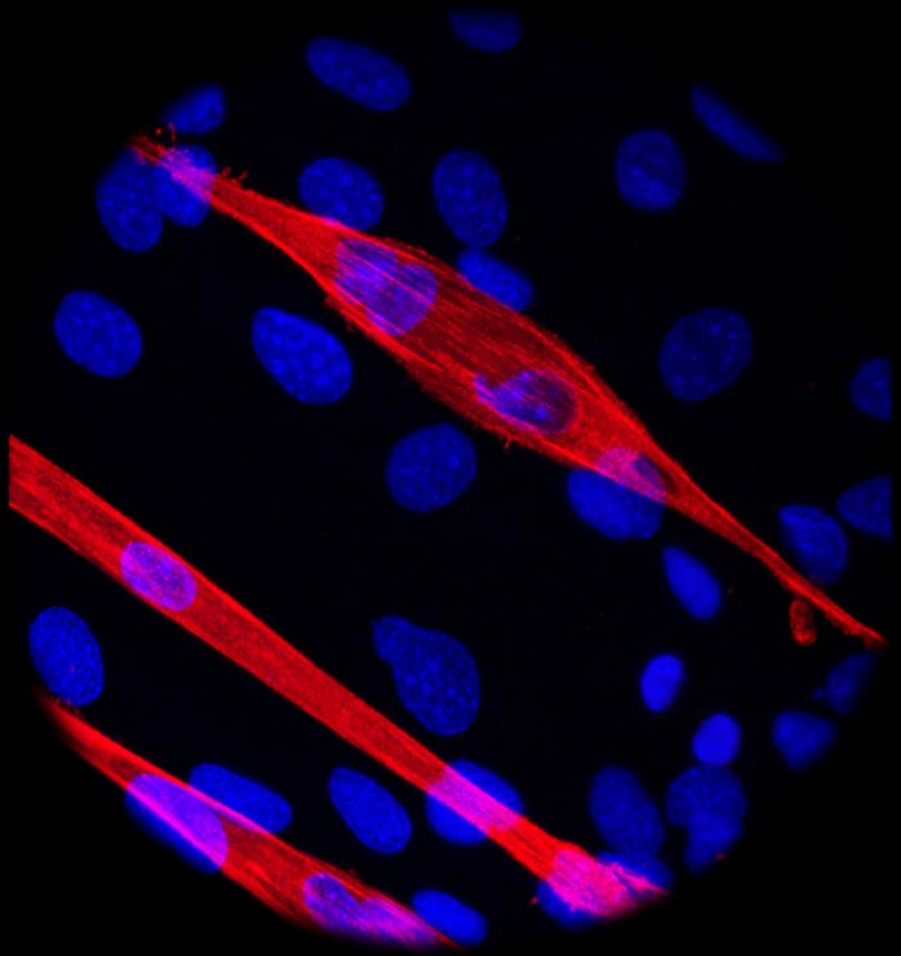




keratinocytes

limbal stem cells





sruiz@aemps.es