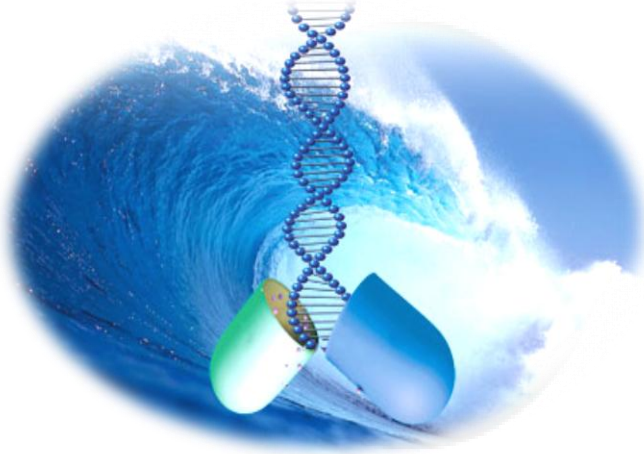
GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

agencia española de medicamentos y productos sanitarios

Medicamentos biológicos
Actualización EMA



Sol Ruiz - AEMPS

Table 8 Top-ten-selling biologic drugs of 2013

Name	Lead company	Molecule type	Approved indication(s)	2013 worldwide sales
Humira (adalimumab)	AbbVie	mAb	RA, juvenile RA, Crohn's disease, PA, psoriasis, ankylosing spondylitis, UC	10,659
Lantus (insulin glargine)	Sanofi	Peptide	Diabetes mellitus type I, diabetes mellitus type II	7,593
Rituxan (rituximab)	Roche	mAb	RA, chronic, lymphocytic leukemia/small cell lymphocytic lymphoma; non-Hodgkin's lymphoma, antineutrophil cytoplasmic antibodies–associated vasculitis, indolent non-Hodgkin's lymphoma, diffuse large B-cell lymphoma	7,500
Remicade (infliximab)	Johnson & Johnson	mAb	RA, Crohn's disease, psoriasis, UC, ankylosing spondylitis, PA	6,962
Avastin (bevacizumab)	Roche	mAb	Colorectal cancer, non–small cell lung cancer, renal cell cancer, brain cancer (malignant glioma; AA and GBM)	6,747
Herceptin (trastuzumab)	Roche	mAb	Breast cancer, gastric cancer	6,558
Gleevec (imatinib)	Novartis	Small molecule	Chronic myelogenous leukemia, gastrointestinal stromal tumor, acute lymphocytic leukemia, hypereosinophilic syndrome, mastocytosis, dermatofibrosarcoma protuberans, myelodysplastic syndrome, myeloproliferative disorders	4,693
Neulasta (pegfilgrastim)	Amgen	Protein	Neutropenia/leukopenia	4,392
Copaxone (glatiramer acetate)	Teva Pharmaceutical	Peptide	Multiple sclerosis	4,356
Revlimid (lenalidomide)	Celgene	Small molecule	Multiple myeloma, myelodysplastic syndrome, mantle cell lymphoma	4,281

mAb, monoclonal antibody; RA, rheumatoid arthritis; PA, psoriatic arthritis; UC, ulcerative colitis; AA, anaplastic astrocytoma; GBM, glioblastoma multiforme. Source: BioMed Tracker

EMA new premises

30 Churchill Place
London E14 5EU

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


"WHAT'S UP, DOC?"

CHMP meeting highlights

EMA >> Committees >> CHMP>> Agendas, minutes and highlights

February 2015

Positive opinion for **Ristempa** (pegfilgrastim), 6mg, solution for injection intended for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy.

January 2015

Positive opinion for **Saxenda** (liraglutide) for weight management in adults who are obese, or those who are overweight and have one or more complications related to their weight, in addition to a reduced-calorie diet and physical activity.

Raplixa (human fibrinogen / human thrombin) received a positive opinion as a supportive treatment where standard surgical techniques are insufficient for the improvement of haemostasis.

CHMP meeting highlights

EMA >> Committees >> CHMP>> Agendas, minutes and highlights

January 2014

The CHMP recommended granting a marketing authorisation for **Eperzan** (albiglutide), for the treatment of type 2 diabetes.

The Committee gave a positive recommendation for **Bemfola** (follitropin alfa), a new biosimilar medicine for the treatment of infertility.

March 2014

The CHMP has recommended the granting of a marketing authorisation for **Sylvant** (siltuximab), a medicine for the treatment of adult patients with multicentric Castleman's disease. Sylvant has an orphan designation and was evaluated by accelerated assessment. Please see the press release in the grid below for more information.

The CHMP also gave a positive recommendation for **Entyvio** (vedolizumab) for the treatment of ulcerative colitis and Crohn's disease. Please see the press release in the grid below for more details.

May 2014

This month the CHMP recommended marketing authorisation for **Gazyvaro** (obinutuzumab) for the treatment of chronic lymphocytic leukaemia. Gazyvaro has an orphan designation. Please see the press release in the grid below for more information.

The Committee recommended approval for **Plegridy** (peginterferon beta-1a) for the treatment of relapsing remitting multiple sclerosis in adults.

The CHMP also gave a positive recommendation for **Nuwiq** (simoctogog alfa) for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

June 2014

Abasria (insulin glargine) received a positive opinion for a marketing authorisation for the treatment of diabetes mellitus. Abasria is the first biosimilar insulin to be recommended for marketing authorisation in the European Union.

July 2014

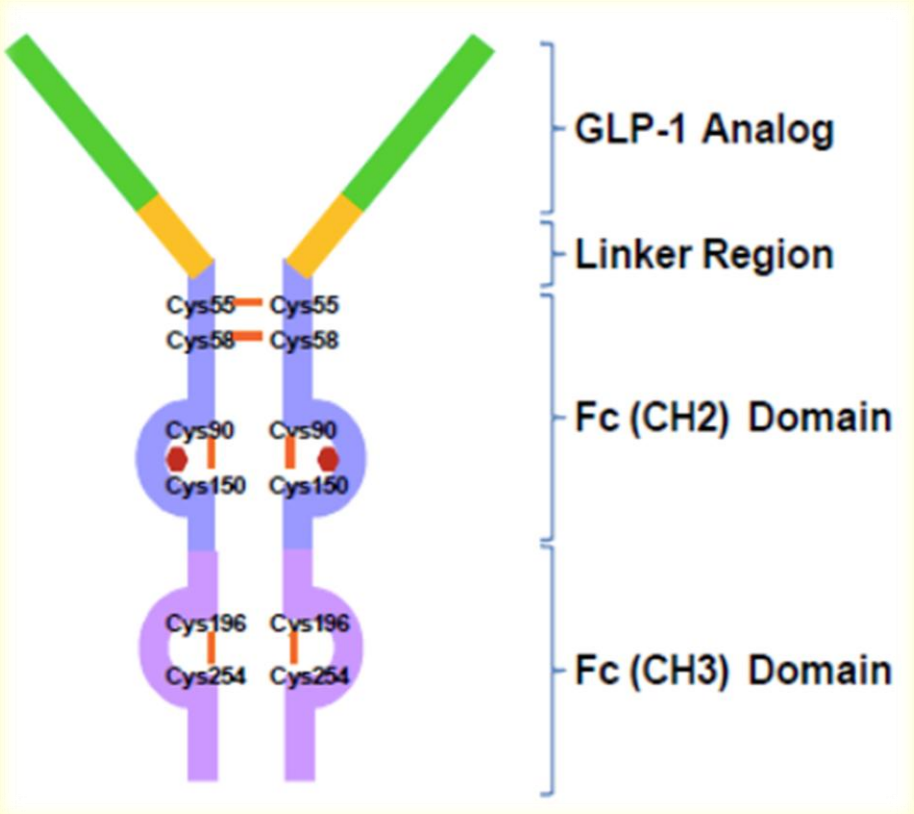
Granting a marketing authorisation to **Xultophy** (insulin degludec/liraglutide) for the treatment of diabetes mellitus has also been recommended.

The CHMP recommended granting a marketing authorisation for **Accofil** (filgrastim), a biosimilar medicine intended for the treatment of neutropenia.

September 2014

Positive opinion for **Egranli** (balugrastim; HSA-G-CSF) for the treatment of chemotherapy-induced neutropenia, **Cyramza** (ramucirumab), orphan medicine for the treatment of gastric cancer, and **Trulicity** (dulaglutide) for the treatment of type 2 diabetes

Positive opinion for **Harvoni** (sofosbuvir / ledipasvir) for the treatment of chronic hepatitis C in adults.



September 2014

Positive opinion for **Egranli** (balugrastim; HSA-G-CSF) for the treatment of chemotherapy-induced neutropenia, **Cyramza** (ramucirumab), orphan medicine for the treatment of gastric cancer, and **Trulicity** (dulaglutide) for the treatment of type 2 diabetes

Positive opinion for **Harvoni** (sofosbuvir / ledipasvir) for the treatment of chronic hepatitis C in adults.

October 2014

Rixubis (nonacog gamma) received a positive opinion for the treatment and prophylaxis of bleeding in patients with haemophilia B.

Positive opinion for **Scenesse** (afamelanotide) for the treatment of erythropoietic protoporphyria (EPP), a rare genetic disease which causes intolerance to light. First medicine for patients with this condition. First time that patients have been involved in CHMP discussions.

November 2014

Cosentyx (secukinumab; anti-IL-17A) recommended by the CHMP as new treatment option for psoriasis.

Positive opinion positive opinions for **Exviera** (dasabuvir) and **Viekirax** (ombitasvir + paritaprevir + ritonavir) for the treatment of chronic hepatitis C

December 2014

Conditional marketing authorisation for the orphan medicine **Holoclar** for the treatment of moderate to severe limbal stem cell deficiency due to physical or chemical burns to the eyes in adults. First advanced therapy medicine containing stem cells to be recommended for approval in the European Union

Next-generation stem cell therapy poised to enter EU market

The European Commission has given a conditional marketing approval for Holoclar, an autologous stem cell therapy for thermal or chemical burns to the eye. With the regulator's go ahead, announced February 20, Holoclar becomes the first stem cell therapy since bone marrow transplantation approved for use in the EU.

"I consider it a very important step towards worldwide implementation of a very promising technology," says Tor Paaske Utheim, an ophthalmologist at the Oslo University Hospital in Norway, who has carried out similar procedures but is not involved in Holoclar. "It is also a very important step in the right direction for other cell therapies."

Holoclar consists of corneal epithelial cells dissociated and expanded *ex vivo*. These cells are taken from a patient's good eye (or from a small healthy section if the damage extends to both eyes) and include limbal stem cells (LSCs), normally responsible for the continuous regeneration and maintenance of the corneal epithelium. Over two to four weeks, the patient's cells are grown at a central laboratory in Italy under good manufacturing practice conditions, and finally grafted onto the limbus—a narrow area located between the cornea and the conjunctiva—in the injured eye (or eyes) to replace the lost stem cells.

Burns or other insults that destroy the limbus result in LSC deficiency. In these situations, epithelial cells from the conjunctiva move to coat the cornea and help protect the eye from the outside. But from the inside they also trigger inflammation, scarring, corneal opacity and, ultimately, blindness and severe pain. Doctors

Thinkstock

Limbal stem cell therapy, Holoclar, could soon be used in Europe to treat ocular burns. A similar product was approved in India in 2008.

1998 and 2007 at clinics in Milan and Rome. The researchers showed that Holoclar produced stable, transparent corneal surfaces in 77% of the eyes (*N. Engl. J. Med.* **363**, 147–155, 2010). In 2013, the team published further results from 152 people treated with Holoclar for burn-related eye damage. The patients were followed for at least five years and showed full symptom abatement and corneal restoration in 66% of eyes and partial improvements in another 19%, with no adverse events related to the cells or their culture components (*Regen. Med.* **8**, 553–567, 2013).

Some trial subjects have been tracked now for 16 years and counting, although 12 months

laboration with Chiesi Pharmaceuticals. Chiesi, which is headquartered in Parma, Italy, also holds the exclusive rights to commercialize Glybera (alipogene tiparvovec), the first gene therapy product approved in the EU (*Nat. Biotechnol.* **30**, 1153, 2012). Andrea Chiesi, CEO of Holostem and director of R&D portfolio management at Chiesi, declined to discuss the specifics of Holoclar's price or market potential ahead of full marketing authorization (see p217).

Various research teams around the world have achieved success rates comparable to those observed with Holoclar using their own autologous LSC products. The group with

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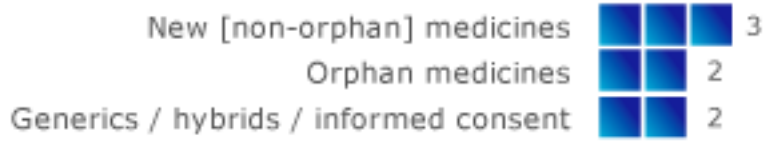
Key CHMP statistics: December 2014

Positive opinions on new medicines



82 Total 2014

Negative opinions on new medicines

3 Total 2014

Positive opinions on extensions of therapeutic indications

39 Total 2014

Withdrawn applications

6 Total 2014

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Experimental Ebola treatments still at early stage of development

Press release

16/12/2014

Experimental Ebola treatments still at early stage of development

For robust scientific assessment more information on safety and efficacy needed

At this point in time there is not enough evidence for any of the experimental therapies for Ebola Virus Disease to draw conclusions on their safety or efficacy when used in Ebola patients. This is the finding of an interim report published by the European Medicines Agency (EMA) that is continuing to review all Ebola treatments currently under development.

Any new information that becomes available will be added to the review to provide the best possible overview of data on medicinal treatments for Ebola.

"Treatments for patients infected with the Ebola virus are still in early stages of development," notes Marco Cavaleri, Head of Anti-infectives and Vaccines at EMA. "We encourage developersto generate more information on the use of these medicines in the treatment of Ebola patients. We will review any new information as soon as it becomes available to support the response to this ongoing public health crisis."

The EMA review was started by the Agency's Committee for Medicinal Products for Human Use (CHMP) to support decision-making by health authorities. This first interim report includes information on seven experimental medicines intended for the treatment of people infected with the Ebola virus:

- BCX4430 (Biocryst);
- Brincidofovir (Chimerix);
- Favipiravir (Fujifilm Corporation/Toyama);
- TKM-100802 (Tekmira);
- AVI-7537 (Sarepta);
- ZMapp (Leafbio Inc.);
- Anti-Ebola F(ab')2 (Fab'entech).

Related content

- Ebola

Related document

Assessment report for Article-5(3) procedure: Medicinal products under development for treatment of Ebola (02/02/2015)

Contact point:

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E-mail: press@ema.europa.eu

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Record number of medicines for rare diseases recommended for approval in 2014

Press release

09/01/2015

Record number of medicines for rare diseases recommended for approval in 2014

Number of medicines with new active substances continues to increase

In 2014, the European Medicines Agency (EMA) recommended the highest number of orphan designated medicines for marketing authorisation in a year. Out of the 82 medicines for human use recommended in 2014, 17 are intended for the treatment of a rare disease, providing therapies for patients who often have only few or no treatment options.

Among them is the first medicine for the treatment of Duchenne muscular dystrophy (Translarna) as well as the first treatment for erythropoietic protoporphyria, a rare genetic disease which causes intolerance to light (Scenesse).

The past year also saw the first recommendation worldwide of a therapy based on stem cells. The orphan medicine (Holoclar) is a treatment for limbal stem cell deficiency (LSCD), a rare eye condition that can result in blindness.

Special regulatory pathways were used for these three medicines (conditional marketing authorisation for Translarna and Holoclar, and approval under exceptional circumstances for Scenesse). These mechanisms are in place to potentially speed up market access for medicines that fulfill unmet medical needs but for which comprehensive data cannot be provided at the time of application for a marketing authorisation.

Eight new medicines for cancer were recommended for marketing authorisation in 2014, of which Lynparza, Imbruvica, Gazyvaro and Cyramza target rare cancers that are difficult to treat. A targeted treatment for melanoma patients whose cancer has a specific mutation was also recommended for approval in 2014 (Mekinist).

Contact point:
Monika Benstetter
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2013	LEMTRADA	Alentuzumab (anti-CD52)	Relapsing remitting MS
	REMSIMA INFLECTRA	Infliximab (anti-TNF)	Same indications as Remicade
	KADCYLA	Trastuzumab emtansine	HER2-positive breast cancer
2014	SYLVANT	Siltuximab (anti-IL-6)	Multicentric Castleman's disease
	ENTYVIO	Vedolizumab (anti-integrin α4β7)	Moderately to severely active Crohn's disease
	GAZYVARO	Obinutuzumab (anti-CD20)	Chronic lymphocytic leukaemia
	CYRAMZA	Ramucirumab	Gastric cancer
	COSENTYX	Secukinumab	Psoriasis

Drugs

Development & Approval Process (Drugs)

- Drug Innovation
- New Molecular Entity Approvals for 2013
- New Molecular Entity Approvals for 2012
- Critical Path Innovation Meetings (CPIM)
- New Molecular Entity Approvals for 2011

Resources for You

- New Molecular Entity Approvals for 2010
- Speeding Access to Important New Therapies
- Access to Investigational Drugs
- CDER New Drug Review: 2011 Update (PDF - 2.7MB)

New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products of 2014

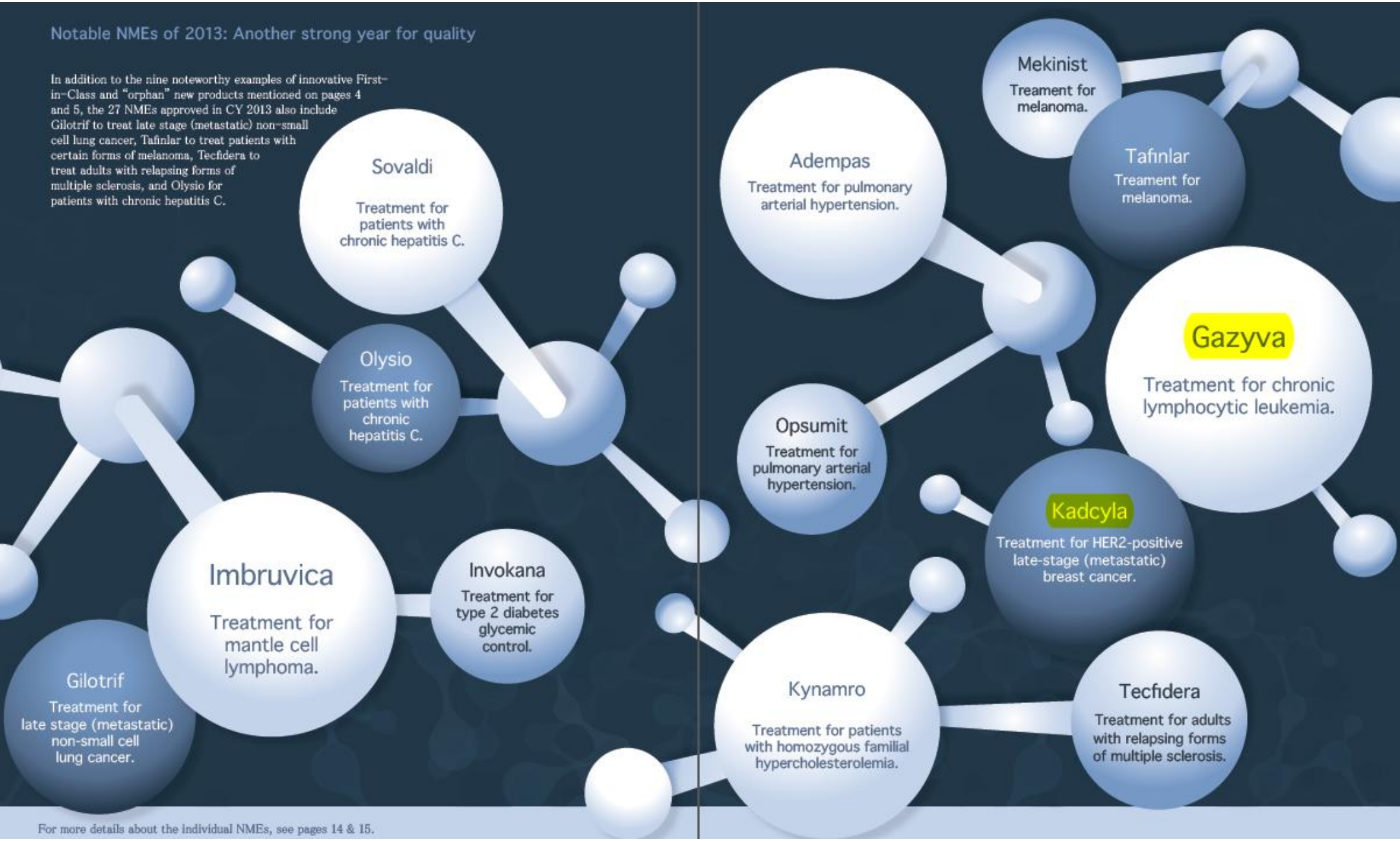
Innovation drives progress. When it comes to innovation in the development of new drugs and therapeutic biological products, FDA's Center for Drug Evaluation and Research (CDER) supports the pharmaceutical industry at every step of the process. With its understanding of the science used to create new products, testing and manufacturing procedures, and the diseases and conditions that new products are designed to treat, FDA provides scientific and regulatory advice needed to bring new therapies to market. The availability of new drugs and biological products often means new treatment options for patients and advances in health care for the American public. For this reason, CDER supports innovation and plays a key role in helping to advance new drug development.

Each year, CDER approves a wide range of new drugs and biological products. Some of these products are innovative new products that never before have been used in clinical practice. Others are the same as, or related to, previously approved products, and they will compete with those products in the marketplace.

Certain drugs are classified as new molecular entities ("NMEs") for purposes of FDA review. Many of these products contain active moieties that have not been approved by FDA previously, either as a single ingredient drug or as part of a combination product; these products frequently provide important new therapies for patients. Some drugs are characterized as NMEs for administrative purposes, but nonetheless contain active moieties that are closely related to active moieties in products that have previously been approved by FDA. For example, CDER classifies biological products submitted in an application under section 351(a) of the Public Health Service Act as NMEs for purposes of FDA review, regardless of whether the Agency previously has approved a related active moiety in a different product. FDA's classification of a drug as an "NME" for review purposes is distinct from FDA's determination of whether a drug product is a "new chemical entity" or "NCE" within the meaning of the Federal Food, Drug, and Cosmetic Act.

Notable NMEs of 2013: Another strong year for quality

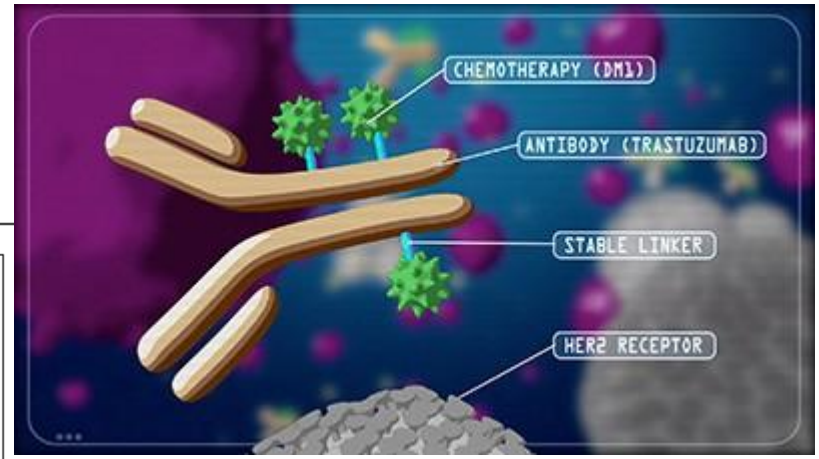
In addition to the nine noteworthy examples of innovative First-in-Class and "orphan" new products mentioned on pages 4 and 5, the 27 NMEs approved in CY 2013 also include Gilotrif to treat late stage (metastatic) non-small cell lung cancer, Tafinlar to treat patients with certain forms of melanoma, Tecfidera to treat adults with relapsing forms of multiple sclerosis, and Olysio for patients with chronic hepatitis C.



For more details about the individual NMEs, see pages 14 & 15.

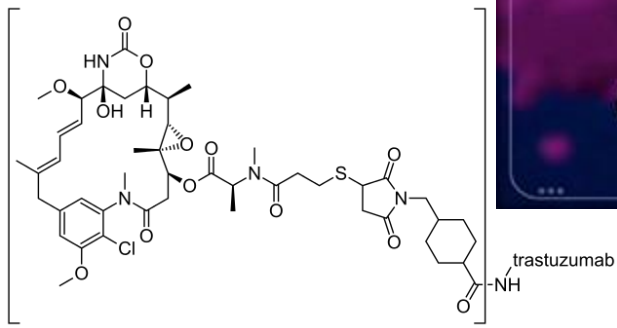
EMA/748315/2013
EMEA/H/C/002389

EPAR summary for the public



Kadcyla

trastuzumab emtansine



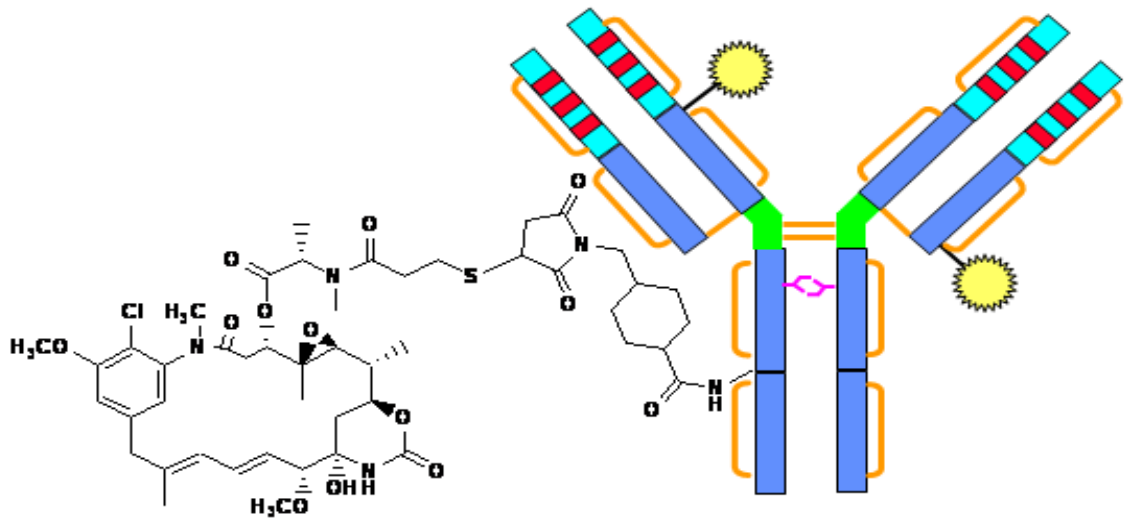
This is a summary of the European public assessment report (EPAR) for Kadcyla. It explains how the Agency assessed the medicine to recommend its authorisation in the EU and its conditions of use. It is not intended to provide practical advice on how to use Kadcyla.

For practical information about using Kadcyla, patients should read the package leaflet or contact their doctor or pharmacist.

What is Kadcyla and what is it used for?

Kadcyla is a cancer medicine that contains the active substance trastuzumab emtansine. It is used to treat advanced or metastatic breast cancer (cancer that has spread to other parts of the body) in adults who previously received trastuzumab and a taxane (type of cancer medicine).

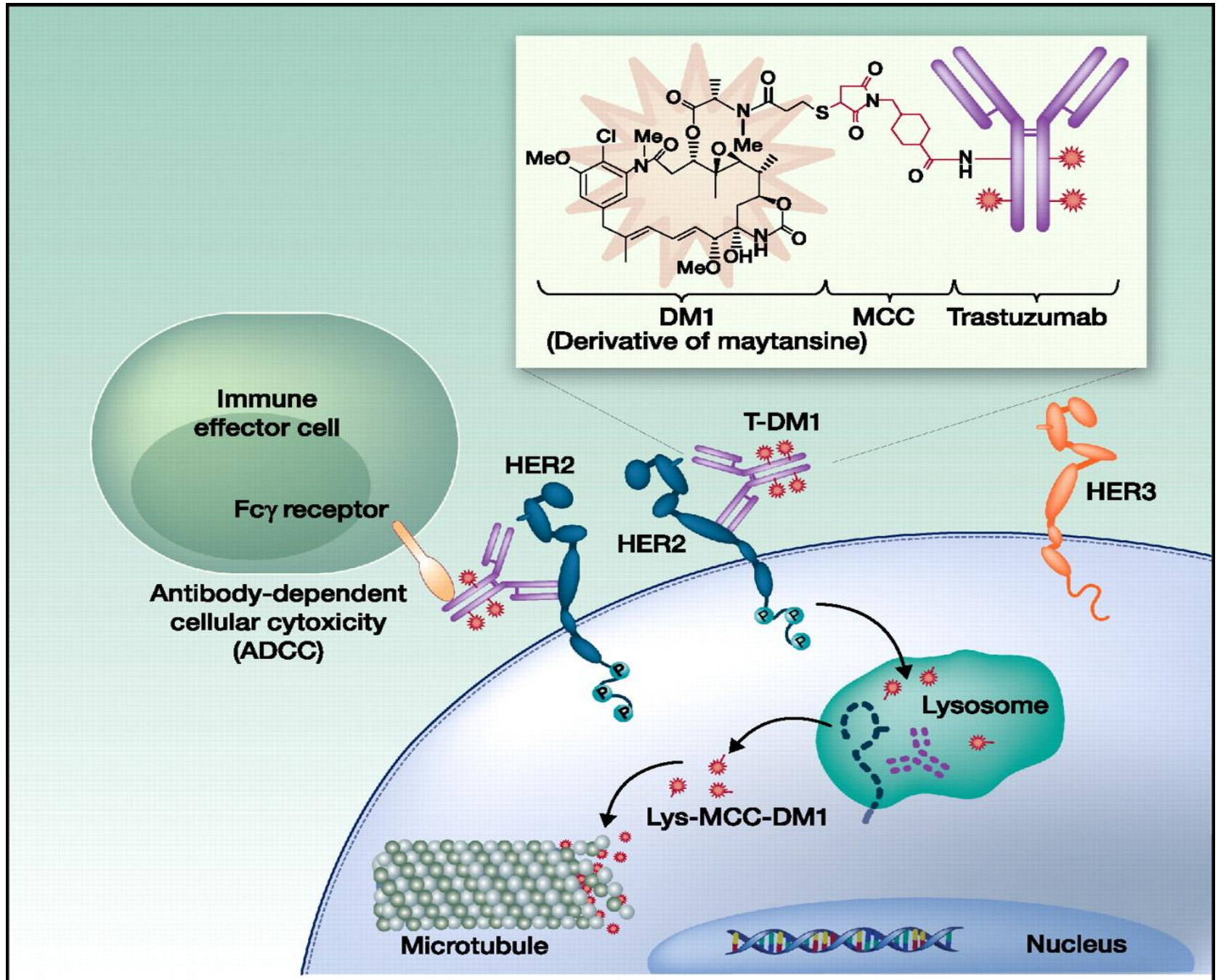
Kadcyla can only be used when the cancer has been shown to 'overexpress HER2': this means that the cancer cell produces on its surface large quantities of a protein which stimulates the growth of the cancer cell and is called HER2 (human epidermal growth factor).



DM1 = (3 to 4 per IgG)

Linker -thioether-

Trastuzumab (HzIgG1) -LysNH_2 (random)



© 2011 American Association for Cancer Research

BWP recent activities

CHMP
PRAC
CVMP
COMP
HMPC
CAT
PDCO
Working parties and other groups
CHMP
Biologics Working Party
Documents
Patients' and Consumers' Working Party
Healthcare Professionals' Working Party
Quality 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);
- 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.

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

Biological guidelines

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
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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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Traditional/enhanced approach
- Process validation/process verification

25 April 2014
EMA/CHMP/BWP/187338/2014
Committee for Medicinal Products for Human Use (CHMP)

Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

Draft

Draft Agreed by Biologics Working Party	April 2014
Adoption by CHMP for release for consultation	25 April 2014
Start of public consultation	1 May 2014
End of consultation (deadline for comments)	31 October 2014

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

Keywords	***active substance, biologics, process validation, process evaluation, process verification, lifecycle***

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 February 2014
EMA/CHMP/BWP/85290/2012
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the declaration of the quantitative composition / potency labelling of biological medicinal products that contain modified proteins as active substance

Draft agreed by Biologics Working Party	February 2013
Agreed by Blood Products Working Party	February 2013
Adopted by Committee for Medicinal Products for Human Use for release for consultation	March 2013
Start of public consultation	March 2013
End of consultation (deadline for comments)	1 October 2013
Agreed by Biologics Working Party	January 2014
Agreed by Blood Products Working Party	January 2014
Adopted by Committee for Medicinal Products for Human Use	20 February 2014
Date for coming into effect	1 September 2014[1]

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 February 2014
EMA/CHMP/CVMP/JEG-3Rs/704685/2012
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper on review and update of EMA guidelines to implement best practice with regard to 3Rs (replacement, reduction and refinement) in regulatory testing of medicinal products

Agreed by JEG 3Rs	October 2013
Adopted by CVMP for release for consultation	12 December 2013
Adopted by CHMP for release for consultation	19 December 2013
Start of public consultation	7 February 2014
End of consultation (deadline for comments)	31 May 2014

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

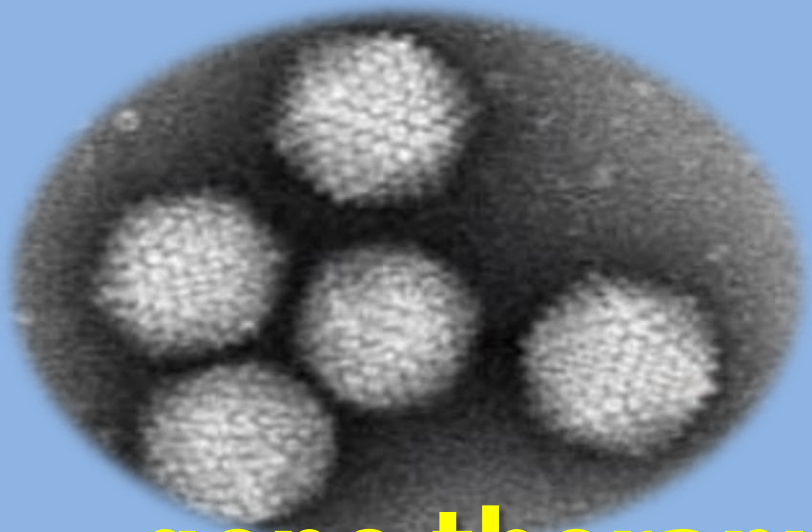
30 May 2013
EMA/CHMP/772061/2013 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for a reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

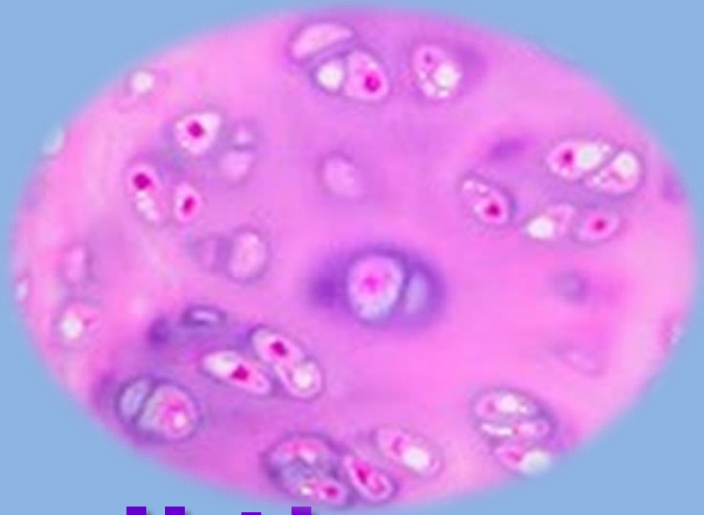
Agreed by Biostatistics Working Party	March 2013
Adoption by CHMP for release for consultation	30 May 2013
Start of public consultation	28 June 2013
End of consultation (deadline for comments)	30 September 2013

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

ATMP in the EU



gene therapy



cell therapy

tissue engineering

07/2007	**CEREPRO**	***AdV-HSVtk*** Withdrawn by the applicant
12/2008	**ADVEXIN**	***AdV-p53*** Withdrawn by the applicant
07/2009	**CHONDROCELECT**	***Autologous chondrocytes***
07/2012	**GLYBERA**	***AAV-LPL***
01/2013	**HYALOGRAFT C AUTOGRAFT**	***Autologous chondrocytes*** Withdrawn by the applicant
03/2013	**ORANERA**	***Autologous oral mucosal epithelial cells***. Withdrawn by the applicant
04/2013	**MACI**	***Matrix-induced autologous chondrocyte implantation***.
06/2013	**PROVENGE**	***Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T)***
12/2014	**HOLOCLAR**	***Ex vivo expanded autologous human corneal epithelial cells containing stem cells***

07/2007	**CEREPRO**	***AdV-HSVtk*** Withdrawn by the applicant
12/2008	**ADVEXIN**	***AdV-p53*** Withdrawn by the applicant
07/2009	**CHONDROCELECT**	***Autologous chondrocytes***
07/2012	**GLYBERA**	***AAV-LPL***
01/2013	**HYALOGRAFT C AUTOGRAFT**	***Autologous chondrocytes*** Withdrawn by the applicant
03/2013	**ORANERA**	***Autologous oral mucosal epithelial cells***. Withdrawn by the applicant
04/2013	**MACI**	***Matrix-induced autologous chondrocyte implantation***. Now suspended
06/2013	**PROVENGE**	***Autologous PBMC activated with PAP-GM-CSF (sipuleucel-T).*** Company declared bankruptcy
12/2014	**HOLOCLAR**	***Ex vivo expanded autologous human corneal epithelial cells containing stem cells***

Overarching biosimilar guidelines

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Topic	Documents	Reference number	Publication date	Effective date	Remarks
Similar biological medicinal products	Draft guideline Concept paper	CHMP/437/04 Rev. 1	Released for consultation May 2013		Deadline for comments 31 October 2013
Similar biological medicinal products	Adopted guideline	CHMP/437/04	September 2005	October 2005	
Revision of the guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins	Concept paper	EMA/275542/2013	Released for consultation March 2014		Deadline for comments 30 June 2014
Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues	Draft guideline Concept paper	EMEA/CHMP/BMWP/42832/2005 Rev. 1	Released for consultation June 2013		Deadline for comments 30 Nov 2013
Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues	Adopted guideline	EMEA/CHMP/BMWP/42832/2005	February 2006	June 2006	
Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues	Overview of comments Adopted guideline Draft guideline Concept paper	EMA/CHMP/BWP/247713/2012	June 2014	December 2014	
Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues	Adopted guideline	EMEA/CHMP/BWP/49348/2005	February 2006	June 2006	

reference

biosimilar


reference
Q S E
biosimilar
comp
studies

Directives 2003/63 - 2004/27

Overarching

Guideline on Similar Biological Medicinal Products

Quality

Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues

Nonclinical & Clinical

Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical & Clinical Issues

Annexes

- EPO
- G-CSF
- Insulin
- IFNα
- IFNβ
- hGH
- FSH
- LMWH
- MAbs

European Medicines Agency
Evaluation of Medicines for Human Use

CHMP/437/04
London, 30 October 2005

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

GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS

DISCUSSION AT THE CHMP	JUNE 2004
ADOPTION BY CHMP	NOVEMBER 2004
RELEASE FOR CONSULTATION	NOVEMBER 2004
DEADLINE FOR COMMENTS	FEBRUARY 2005
DISCUSSION AT WORKING PARTIES	JUNE 2005
ADOPTION BY CHMP	SEPTEMBER 2005
DATE FOR COMING INTO EFFECT	30 OCTOBER 2005

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2014
CHMP/437/04 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products

Draft agreed by Biosimilar Medicinal Products Working Party and Biologics Working Party	March 2013
Adopted by CHMP for release for consultation	25 April 2013
Start of public consultation	30 April 2013
End of consultation (deadline for comments)	31 October 2013
Revised draft agreed by Biosimilar Medicinal Products Working Party and Biologics Working Party	July 2014
Adoption by CHMP	23 October 2014
Date for coming into effect	30 April 2015*

* After adoption by CHMP applicants may apply some or all provisions of this guideline in advance of this date.

European Medicines Agency
Evaluation of Medicines for Human Use

2005

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2015

- Clear definition of a biosimilar
- Scientific principles as outlined in ICH Q5E

- Aplicable to any biological product*
- Same posology and RoA

- Differences in strength, pharmaceutical form and formulation can be justified
- Extrapolation of indications possible
- No need to repeat demonstration of biosimilarity

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SCIENCE MEDICINES HEALTH

2015

- The active substance of a biosimilar must be similar, in molecular and biological terms, to the active substance of the reference medicinal product. For example, for an active substance that is a protein, the amino acid sequence is expected to be the same.
- The posology and route of administration of the biosimilar must be the same as those of the reference medicinal product.
- Deviations from the reference product as regards strength, pharmaceutical form, formulation, excipients or presentation require justification. If needed, additional data should be provided. Any difference should not compromise safety.
- Intended changes to improve efficacy (e.g. glycooptimisation) are not compatible with the biosimilarity approach. However, differences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) should be addressed, but may not preclude biosimilarity.

3.3. Principles of establishing biosimilarity

The guiding principle of a biosimilar development programme is to establish similarity between the biosimilar and the reference product by the best possible means, ensuring that the previously proven safety and efficacy of the reference medicinal product also applies to the biosimilar.

A biosimilar should be highly similar to the reference medicinal product in physicochemical and biological terms. Any observed differences have to be duly justified with regard to their potential impact on safety and efficacy.

A stepwise approach is normally recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation. The extent and nature of the non-clinical *in vivo* studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s) including the robustness of the physicochemical, biological and non-clinical *in vitro* data.

The ultimate goal of the biosimilar comparability exercise is to exclude any relevant differences between the biosimilar and the reference medicinal product. Therefore, studies should be sensitive enough with regard to design, conduct, endpoints and/or population to detect such differences.

European Medicines Agency

June 2005
CPMP/ICH/5721/03

ICH Topic Q 5 E
Comparability of Biotechnological/Biological Products

1.4 *General Principles*

The goal of the comparability exercise is to ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes.

The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2014
EMEA/CHMP/BMWP/42832/2005 Rev1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

Draft agreed by Biosimilar Medicinal Products Working Party (BMWP)	April 2013
Adopted by CHMP for release for consultation	30 May 2013
Start of public consultation	03 June 2013
End of consultation (deadline for comments)	30 November 2013
Agreed by Biosimilar Medicinal Products Working Party (BMWP)	October 2014
Adopted by CHMP	18 December 2014
Date for coming into effect	01 July 2015

This guideline replaces 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues' (EMEA/CHMP/BMWP/42832/2005).

Executive summary

The *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* (EMEA/CHMP/BMWP/42832/05 Rev.1) lays down the non-clinical and clinical requirements for a similar biological medicinal product ("biosimilar").

The non-clinical section addresses the pharmaco-toxicological assessment. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, and efficacy studies. The section on clinical safety and pharmacovigilance addresses clinical safety studies, including immunogenicity, as well as the risk management plan.

The current revision covers the following topics: a stepwise approach for the design of non-clinical studies; the use of pharmacodynamic markers; study design, choice of appropriate patient population and choice of surrogate and clinical endpoints in efficacy trials; clinical safety (including design of immunogenicity studies), risk management plan, and pharmacovigilance, and extrapolation of safety and efficacy. The guideline recommends a stepwise conduct of non-clinical and clinical studies.

NON-CLINICAL STUDIES

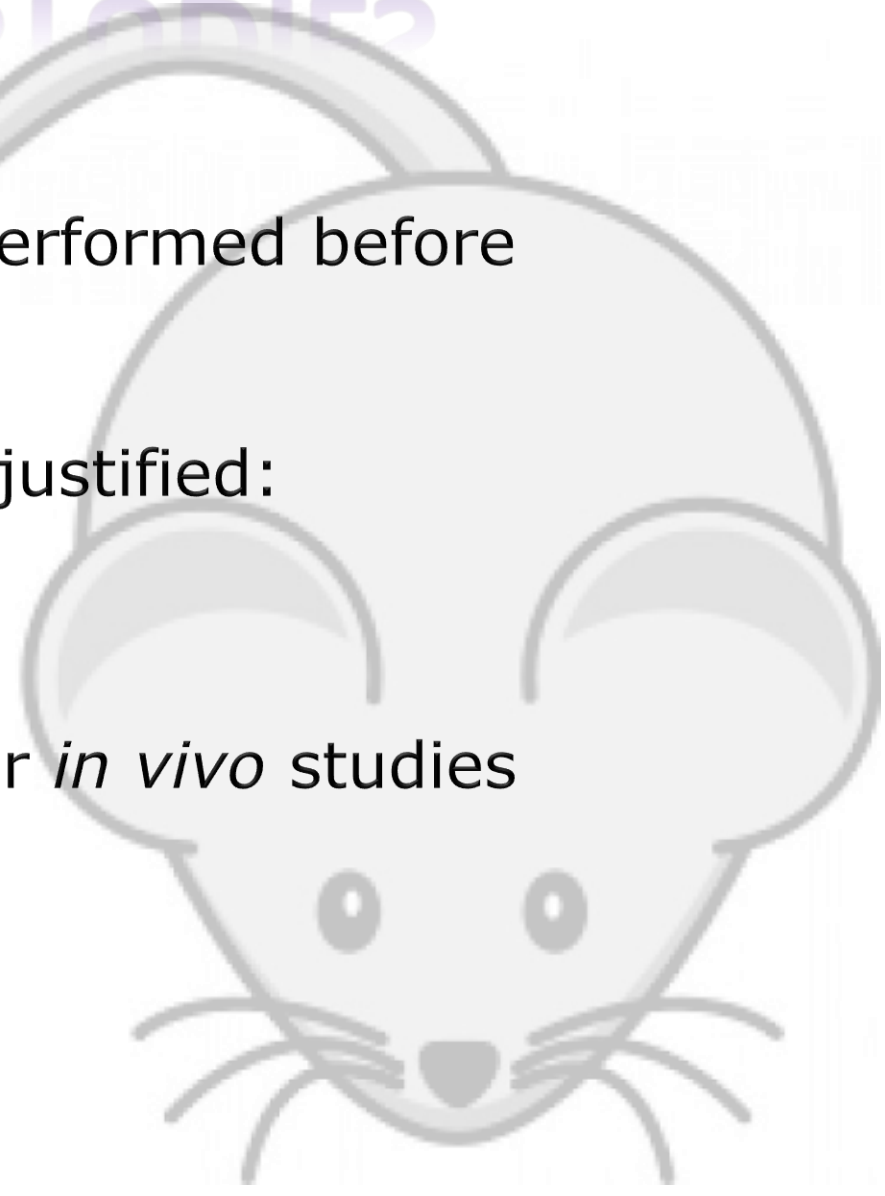
Non-clinical studies should be performed before initiating clinical trials.

Step-wise approach; should be justified:

① *in vitro* studies

② Determination of the need for *in vivo* studies

③ *in vivo* studies



Additional *in vitro* studies:

- Binding to target antigen(s)
- Binding to representative isoforms of the relevant three Fc gamma receptors (FcγRI, FcγRII and FcγRIII), FcRn and complement (C1q)
- Fab-associated functions (e.g. neutralization of a soluble ligand, receptor activation or blockade)
- Fc-associated functions (e.g. antibody-dependent cell-mediated cytotoxicity, ADCC; complement-dependent cytotoxicity, CDC; complement activation)

These studies should be comparative in nature and designed to be sensitive enough to detect differences in the concentration–activity relationship

Step 1: PK/PD
Step 2: E & S

E & S

- Adequately powered, randomised, parallel group comparative clinical trial, preferably double-blind, normally equivalence trials.
- Deviation from guidelines should be justified
- Most sensitive patient population and clinical EP preferred
- Comparative S data (immunogenicity)
- Extrapolation of indications: possible based on the overall evidence of comparability

6. Extrapolation of efficacy and safety from one therapeutic indication to another

The reference medicinal product may have more than one therapeutic indication. When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable, but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required. Extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by *in vitro* functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication. Additional data are required in certain situations, such as

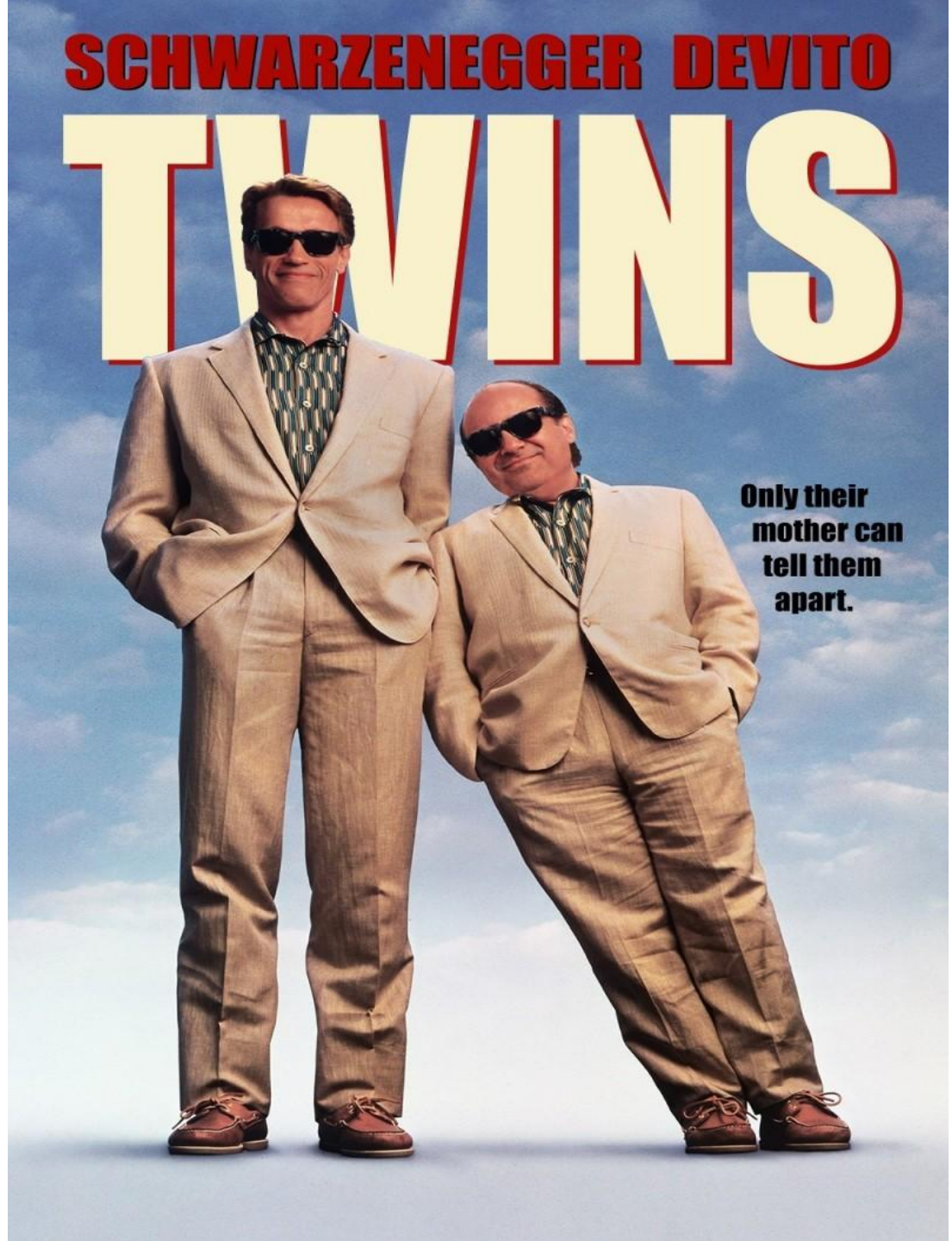
1. the active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications
2. the active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications
3. the studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety.

Immunogenicity is related to multiple factors including the route of administration, dosing regimen, patient-related factors and disease-related factors (e.g. co-medication, type of disease, immune status). Thus, immunogenicity could differ among indications. Extrapolation of immunogenicity from the studied indication/route of administration to other uses of the reference product should be justified.

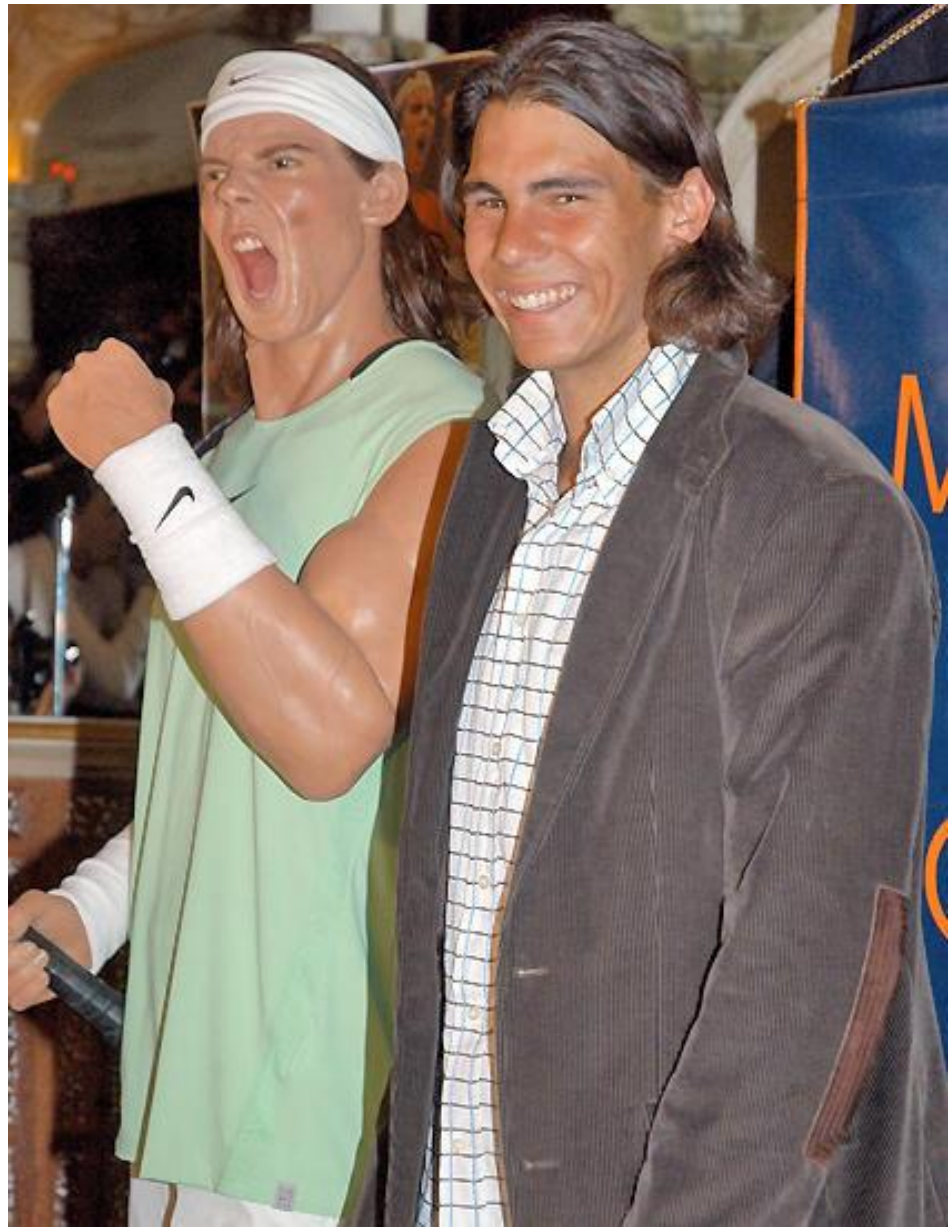
biosimilars

13/03/2015

Medicine Name	Active Substance	Status	Authorisation date
Abasaglar (prev Abasria)	insulin glargine	Authorised	09/09/2014
Abseamed	epoetin alfa	Authorised	28/08/2007
Accofil	filgrastim	Authorised	18/09/2014
Alpheon	rhIFN alfa-2a	Refused	-
Bemfola	follitropin alfa	Authorised	27/03/2014
Binocrit	epoetin alfa	Authorised	28/08/2007
Biograstim	filgrastim	Authorised	15/09/2008
Epoetin Alfa Hexal	epoetin alfa	Authorised	28/08/2007
Filgrastim Hexal	filgrastim	Authorised	06/02/2009
Filgrastim ratiopharm	filgrastim	Withdrawn	15/09/2008
Grastofil	filgrastim	Authorised	18/10/2013
Inflectra	infliximab	Authorised	10/09/2013
Nivestim	filgrastim	Authorised	08/06/2010
Omnitrope	somatropin	Authorised	12/04/2006
Ovaleap	follitropin alfa	Authorised	27/09/2013
Ratiograstim	filgrastim	Authorised	15/09/2008
Remsima	infliximab	Authorised	10/09/2013
Retacrit	epoetin zeta	Authorised	18/12/2007
Silapo	epoetin zeta	Authorised	18/12/2007
Tevagrastim	filgrastim	Authorised	15/09/2008
Valtropin	somatropin	Withdrawn	24/04/2006
Zarzio	filgrastim	Authorised	06/02/2009


SCHWARZENEGGER DEVITO
TWINS
Only their mother can tell them apart.


7




ALMOST IDENTICAL

Thank you!

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