2014 Año de la Biotecnología en España

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

Agencia Española de Medicamentos y Productos Sanitarios

EVALUACION DE MEDICAMENTOS BIOLOGICOS EN LA EMA

UIMP 2014

Sol Ruiz - AEMPS

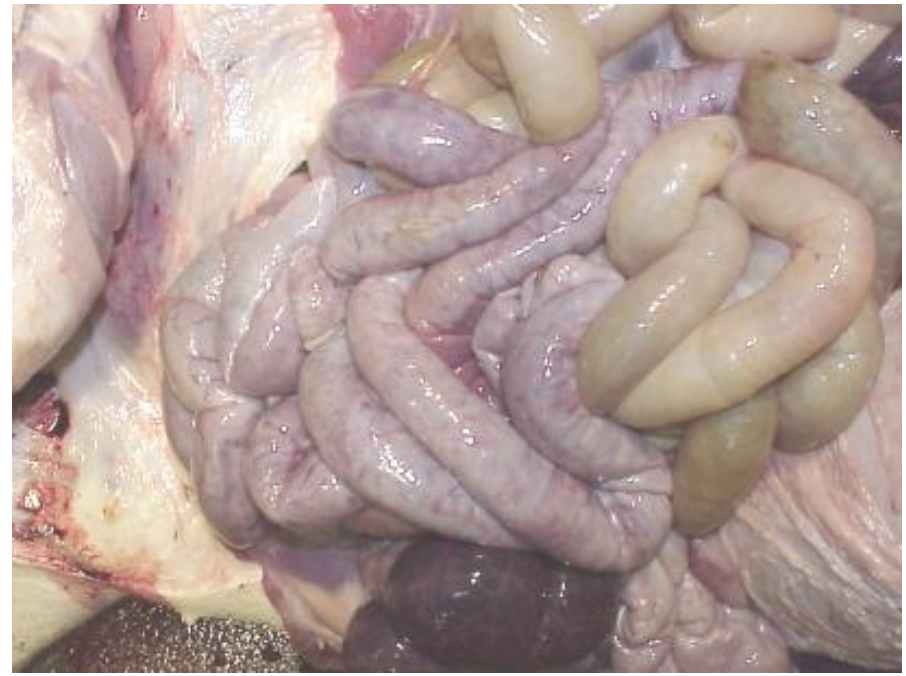
Biologicals

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

bioactivity and immunogenicity are dependent upon all its *structural features*

COMMISSION DIRECTIVE 2003/63/EC of 25 June 2003



HEPARIN SODIUM INJECTION, USP

5,000

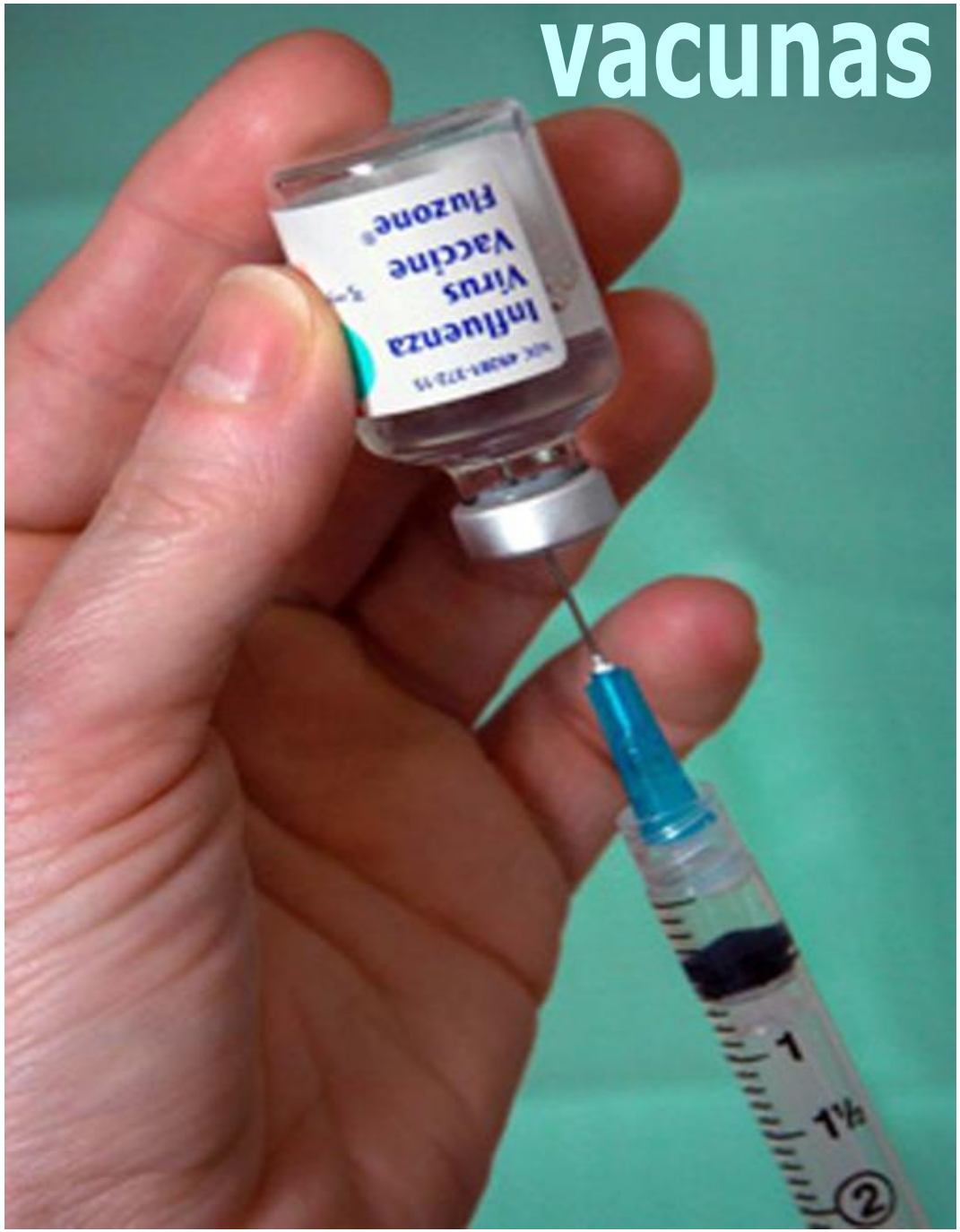
USP Units/mL

(Derived from Porcine Intestinal Mucosa)

For IV or SC Use

Rx only

1 mL Multiple Dose Vial


vacunas
influenza
Virus
Vaccine
fluzone®


albumin
human 20% octapharma
50ml
Infusion solution for
intravenous use only.
albumin
hemoderivados


Humulina Regular
1 vial de 10 ml
917476
TLD
Humulina
Biotecnológicos

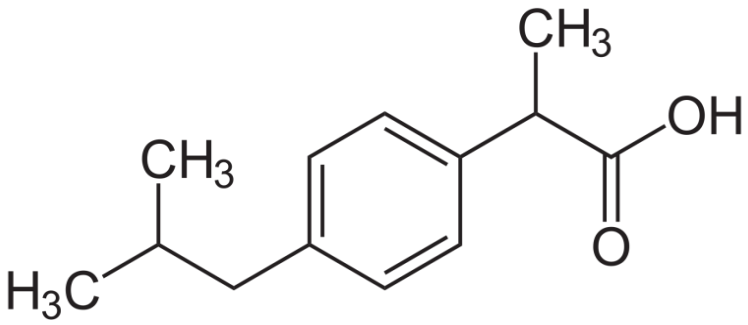
Chemical med product

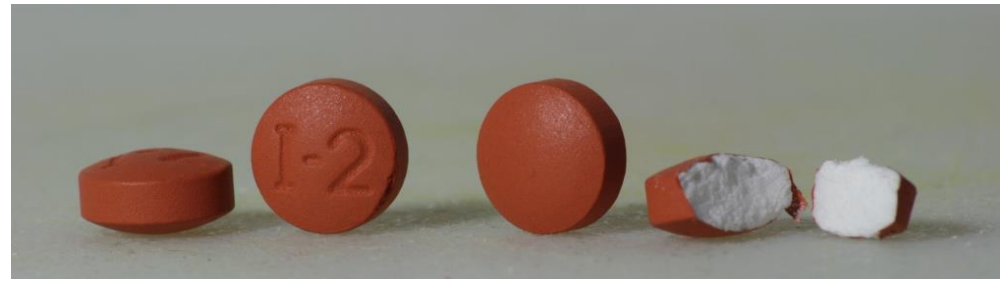
well defined molecular structure, easy to characterize

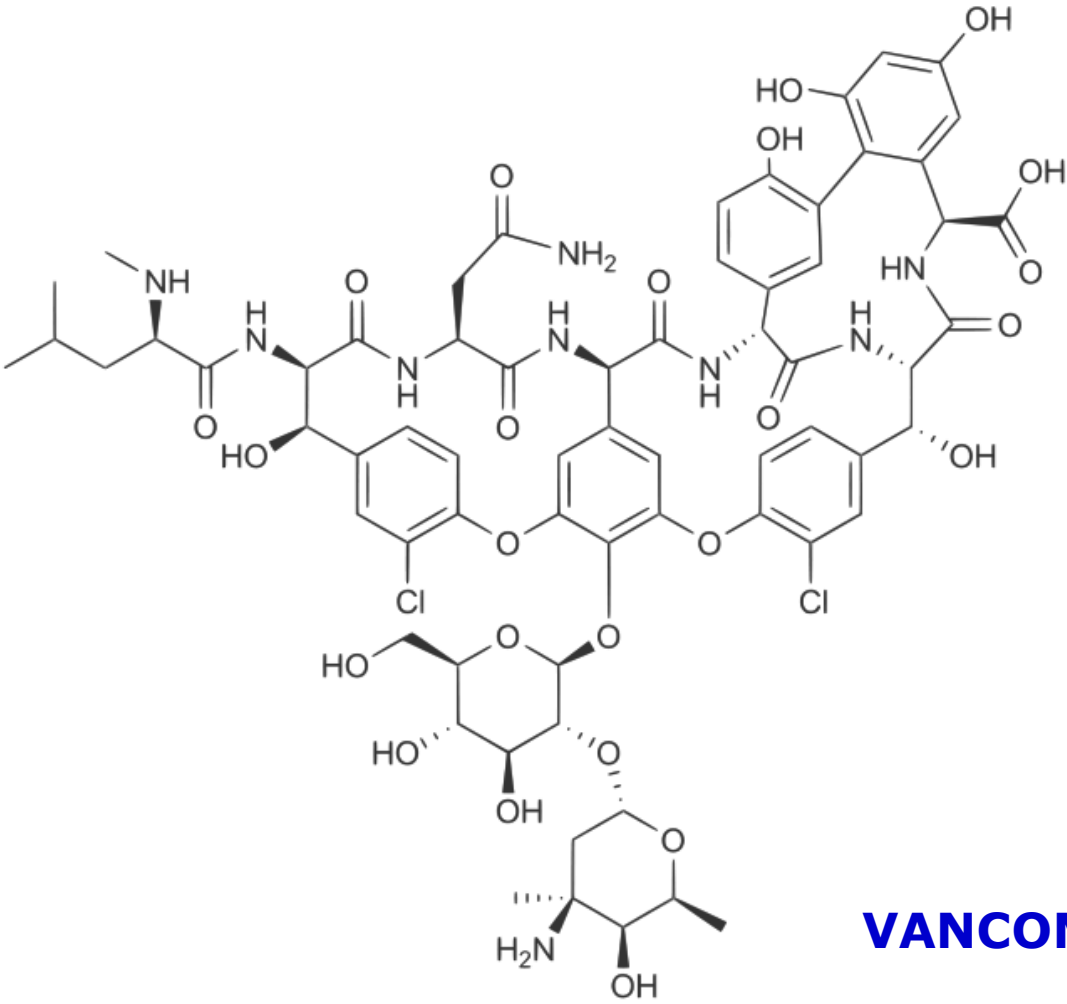
impurity profile related to synthesis and degradation routes

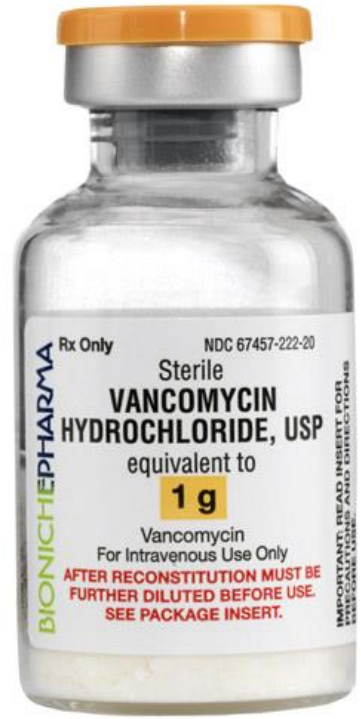
safety and efficacy are independent of the origin of the product

IBUPROFENO (mol. mass **206.29** g/mol)



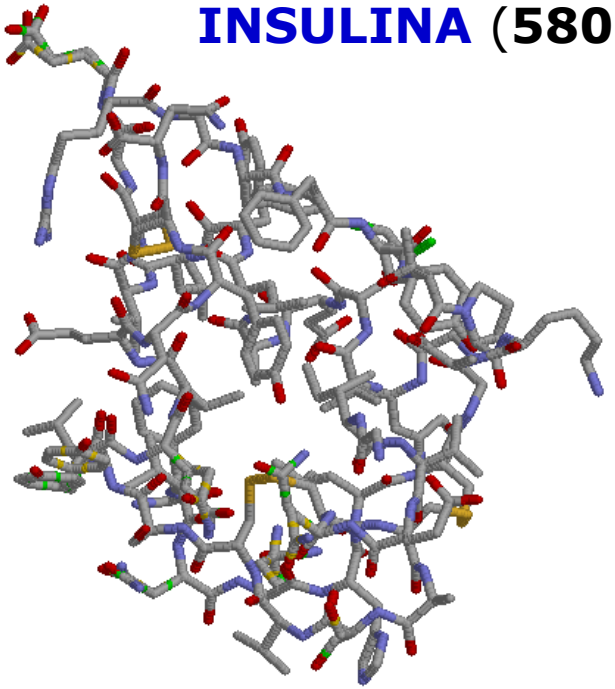


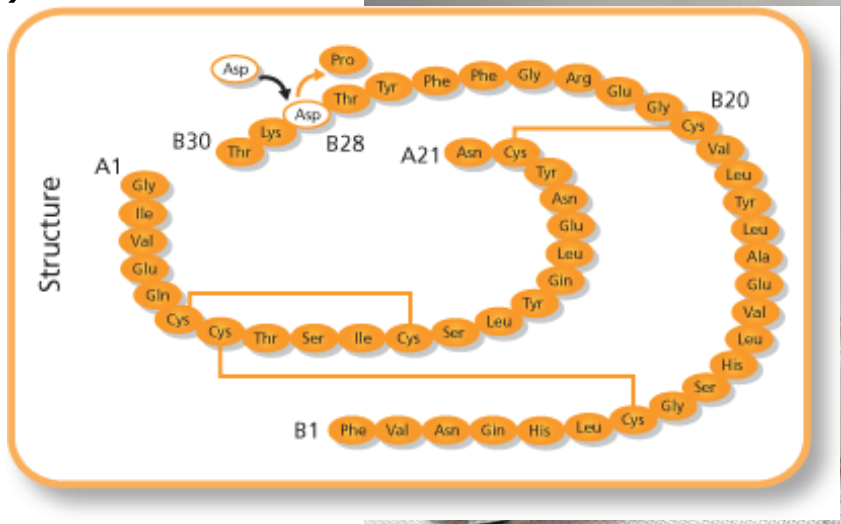


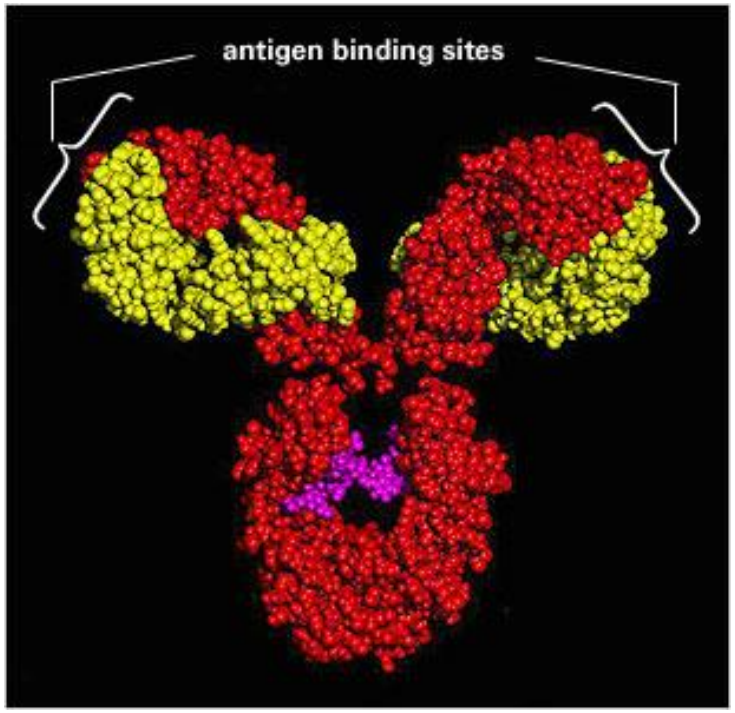


VANCOMICINA (mol. mass **1449.3** g/mol)

INSULINA (**5808 Da**)

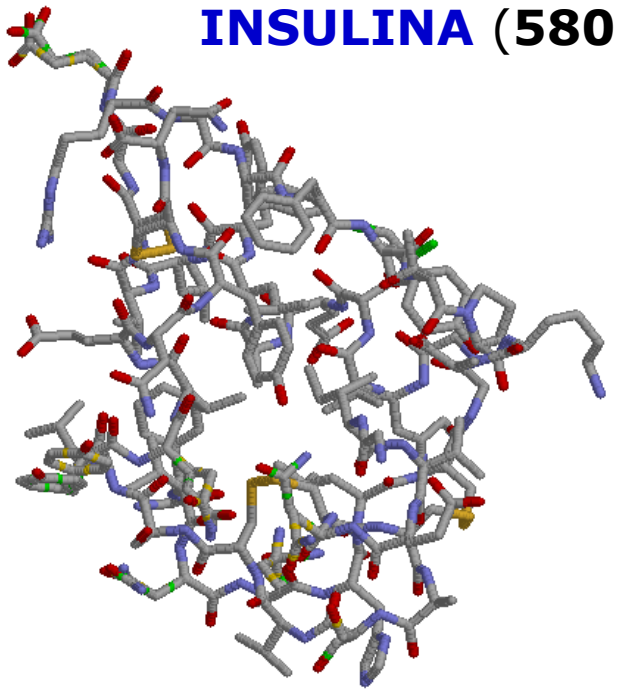


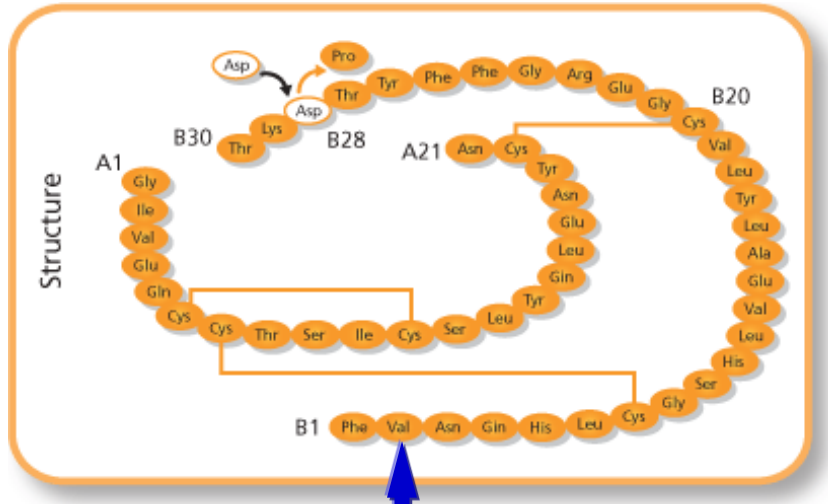


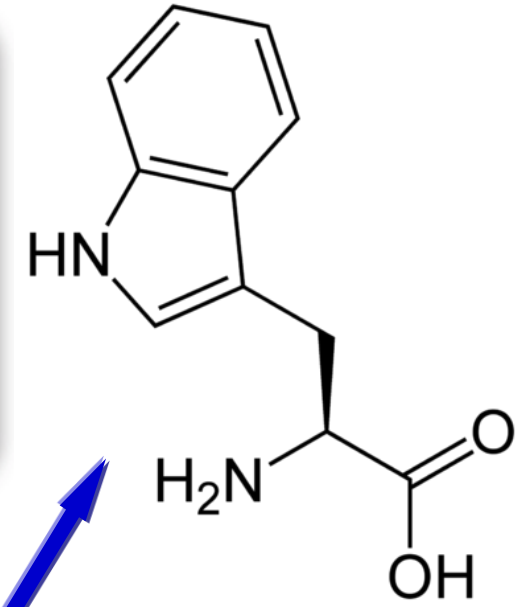


MoAb (**150 000 Da**)

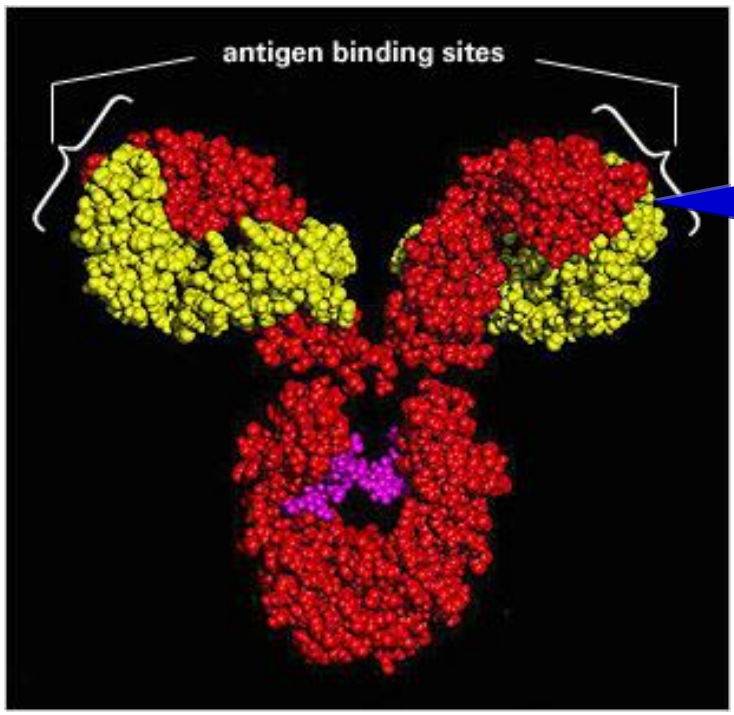
INSULINA (**5808 Da**)

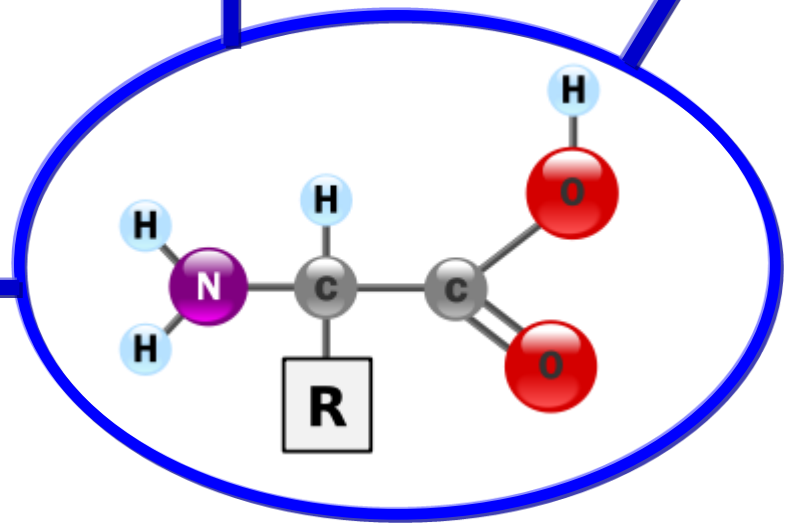




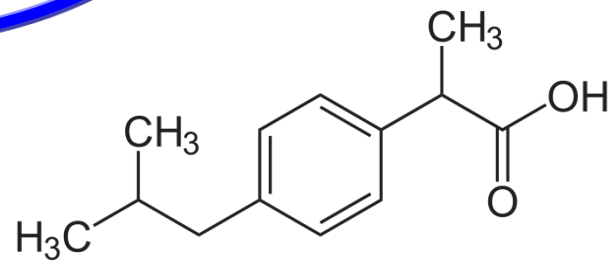


Trp
(204.23
g/mol)



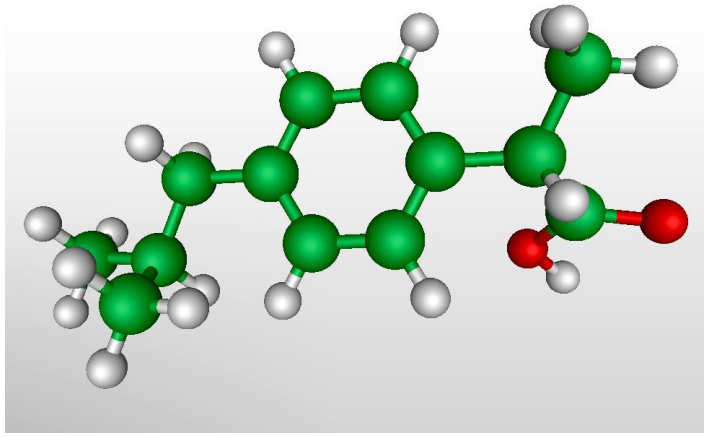


MoAb (**150 000 Da**)

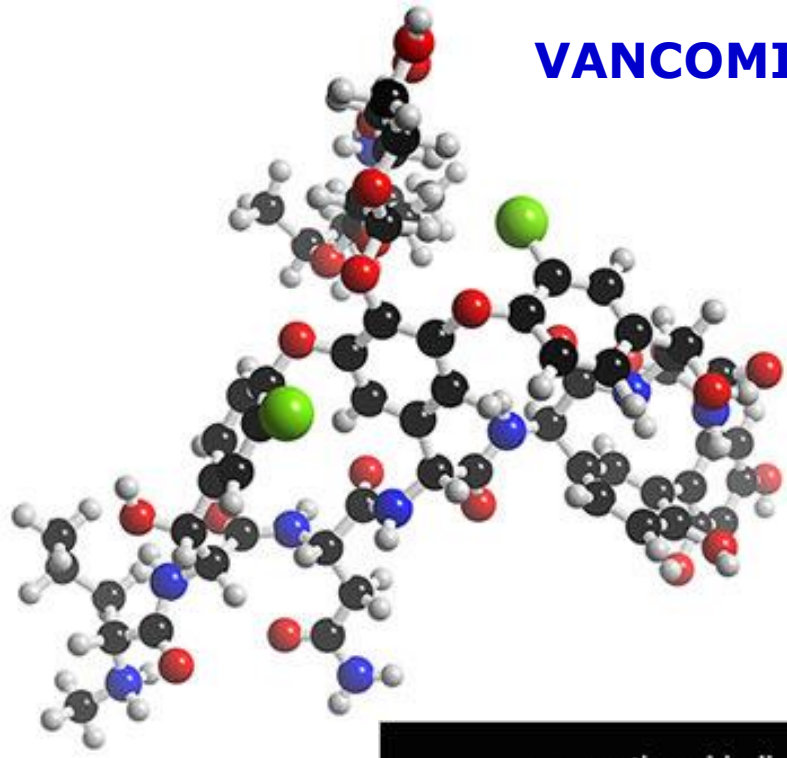


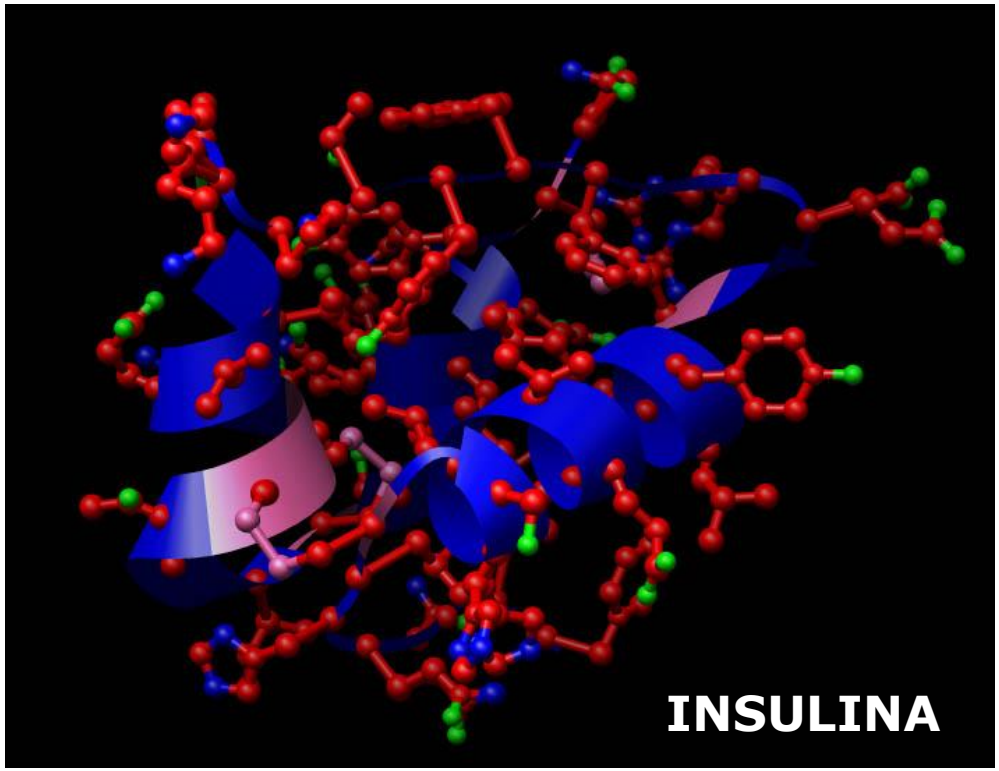
206.29 g/mol

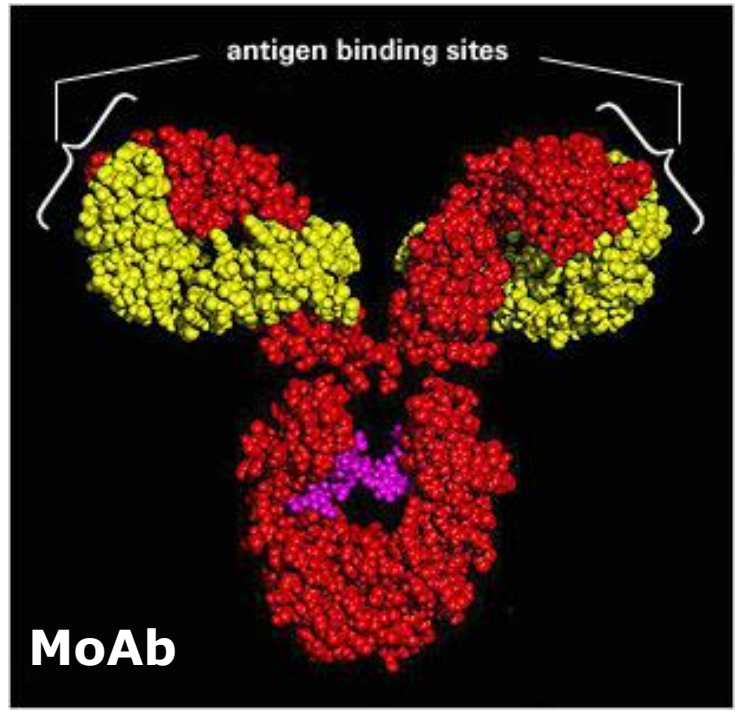
IBUPROFENO



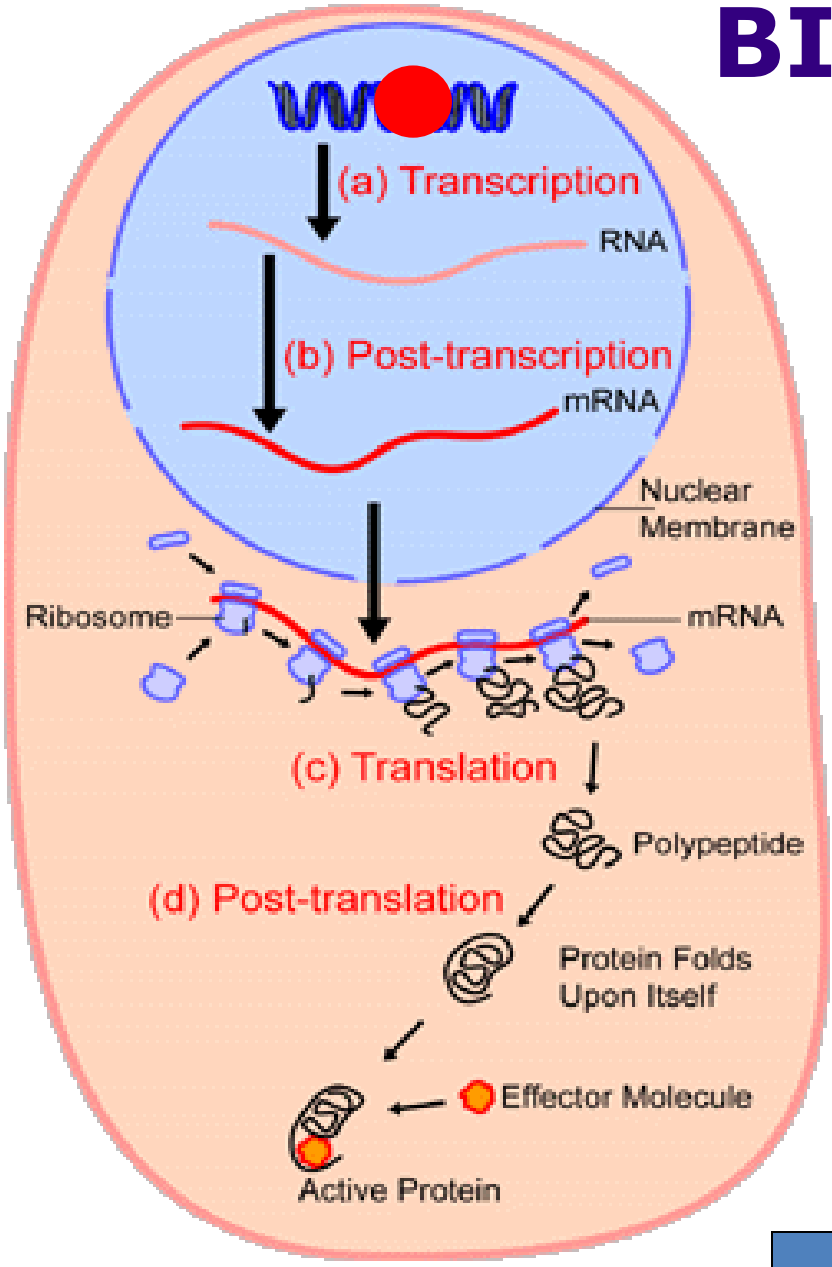
VANCOMICINA

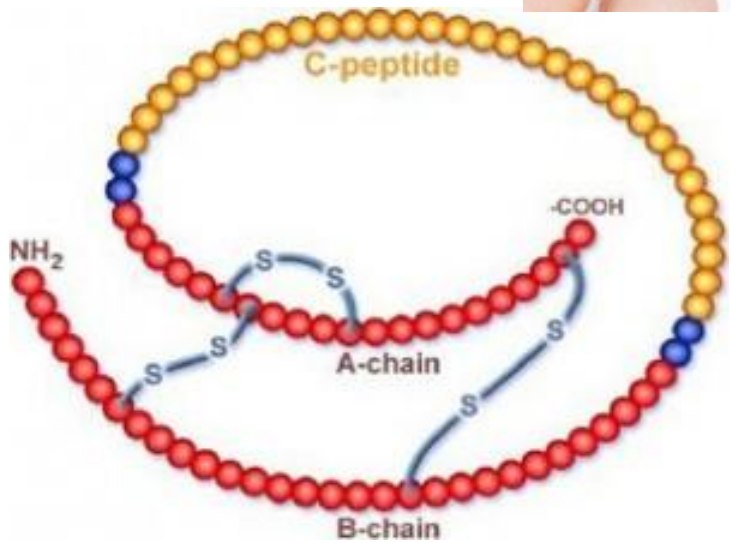






BIOTECNOLÓGICOS





PROTEÍNAS RECOMBINANTES

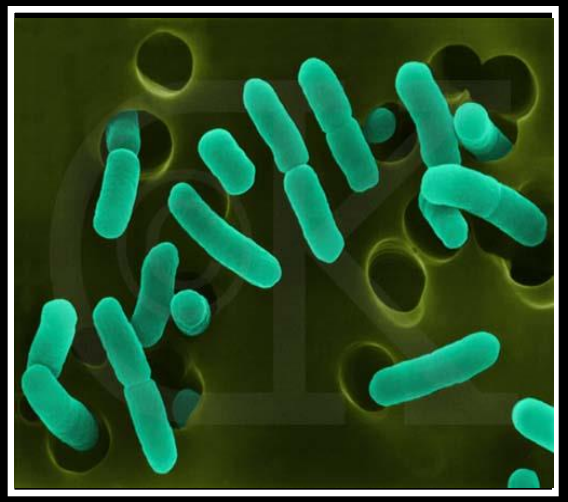
i) Idénticas a la molécula natural

- Insulina*
- Hormona de crecimiento

ii) Moléculas modificadas/nuevas

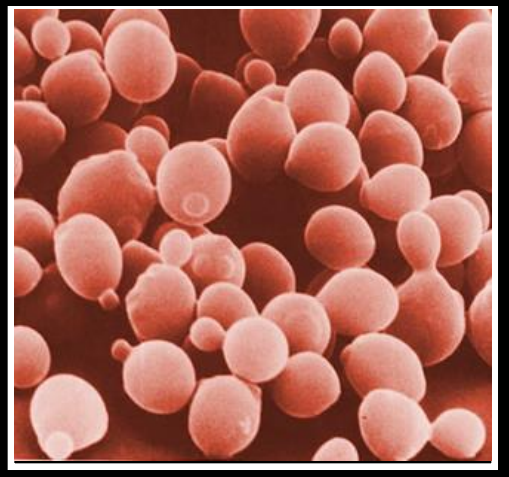
- Proteínas de fusión (TNFR:Fc)
- Anticuerpos monoclonales “humanizados”

host



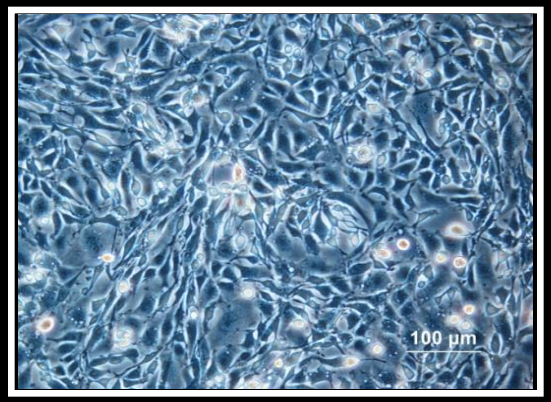
Bacteria

E. coli



Yeast

Saccharomyces

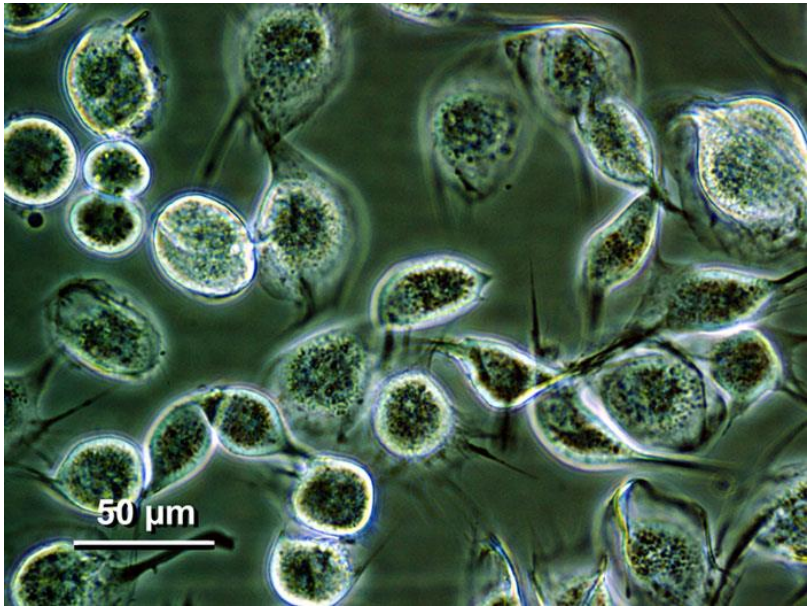


Mammalian cell lines

CHO *(Chinese hamster ovary)*

NS0 *(murine myeloma)*

cell



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 (EMEA) 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 EMEA altered its position, after a more detailed review of the data, because it wanted to convey its support to industry for this bioprocessing method.

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

EMEA'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 EMEA, it could provide clinical data on just 19 cases—five surgical patients, nine pregnant women and five 'compassionate use' cases. Citing dosing inconsistencies, the EMEA disqualified all but the five surgical cases, leaving a number far below the minimum 12 cases

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 opinion[1] (initial authorisation)

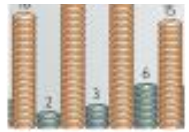
Ruconest

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.

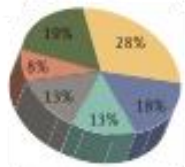
They may request a re-examination of any CHMP opinion, provided they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

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.



2010 FDA approvals p82

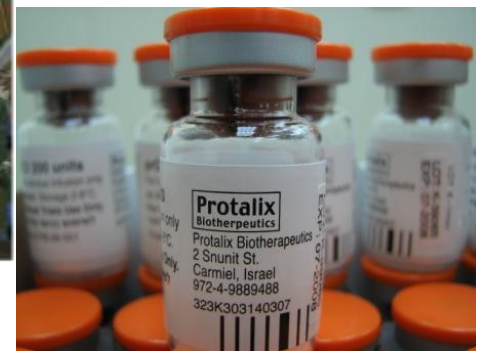
Guidance on co-developing investigational drugs p86



Causes of Phase III failures p87

Abraham Thomas discusses obesity drugs p90

Market for hepatitis C drugs p93



‘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

News & Events

FDA NEWS RELEASE

For Immediate Release: Jan. 16, 2013
Media Inquiries: Rita Chappelle, 301-796-4672, rita.chappelle@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA, OCOD@fda.hhs.gov

FDA approves new seasonal influenza vaccine made using novel technology

The U.S. Food and Drug Administration today announced that it has approved Flublok, the first trivalent influenza vaccine made using an insect virus (baculovirus) expression system and recombinant DNA technology. Flublok is approved for the prevention of seasonal influenza in people 18 through 49 years of age.

Unlike current flu vaccines, Flublok does not use the influenza virus or eggs in its production. Flublok's novel manufacturing technology allows for production of large quantities of the influenza virus protein, hemagglutinin (HA) – the active ingredient in all inactivated influenza vaccines that is essential for entry of the virus into cells in the body. The majority of antibodies that prevent influenza virus infection are directed against HA. While the technology is new to flu vaccine production, it is used to make vaccines that have been approved by the FDA to prevent other infectious diseases.

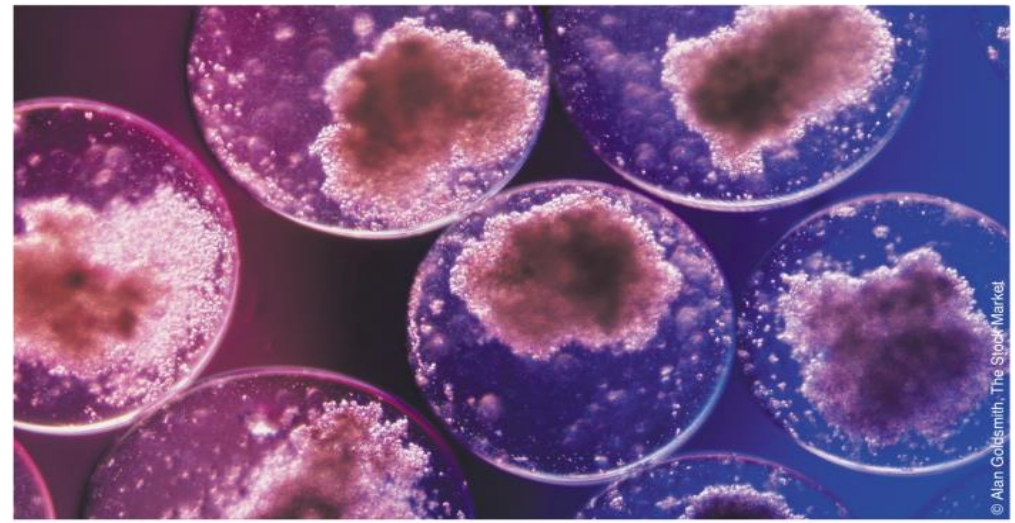
"This approval represents a technological advance in the manufacturing of an influenza vaccine," said Karen Midthun, M.D., director of the FDA's Center for Biologics Evaluation and Research. "The new technology offers the potential for faster start-up of the vaccine manufacturing process in the event of a pandemic, because it is not dependent on an egg supply or on availability of the influenza virus."

Monoclonal antibodies in the clinic

Despite initial teething problems, the number of clinically effective monoclonal antibodies is growing.

Janice M. Reichert

Monoclonal antibodies (mAbs) are nature's biological warheads, able to target and help eliminate foreign or abnormal agents from the body. In theory, replicating this powerful defense system could cure some of humanity's most deadly diseases. Indeed, when these biologics first entered clinical studies in the early 1980s they were heralded as "magic bullets" for the treatment of cancers, able to seek out and destroy tumor cells. However, early studies were disappointing and since then mAbs have fallen in and out of fashion. Today, 10 mAbs are now approved as therapeutics in the United States, so some of the original enthusiasm appears to have been justified. Here, a retrospective study provides a picture of the success of mAbs in the clinic, and prompts speculation about the most suitable choice of mAb class to pursue as a therapeutic.



Hybridomas were the original source of monoclonal antibodies for clinical trials.

The monoclonal revolution

The first generation of mAbs, unveiled in 1975 (ref. 1), were murine mAbs derived from mouse B-cell hybridomas (see "Monoclonal antibodies by design"). However, as murine mAbs moved into clinical trials, it became clear that they had limited potential as therapeutics. The human immune system recognizes murine mAbs as foreign material, producing human anti-mouse antibodies (HAMAs) to clear them from the body, thereby limiting their therapeutic benefit. Furthermore, murine mAbs are inefficient at triggering human effector functions and are more prone to HAMA reactions.

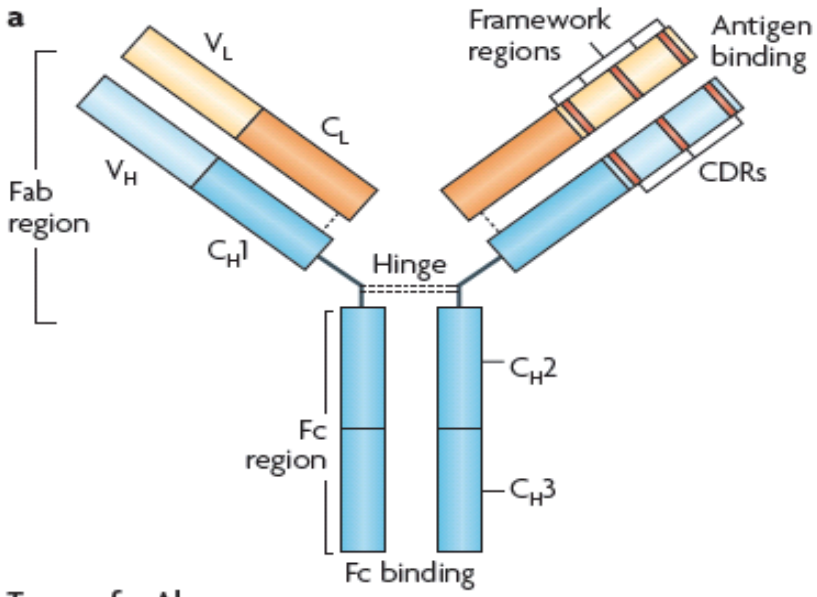
If mAbs were to become a class of successful therapeutics, then researchers needed to create nonimmunogenic mAbs with high binding affinities that could trigger the appropriate effectors. The most obvious strategy was to make mAbs more "humanlike" by creating mAbs with human protein sequences. Human hybridomas were produced using the same methods applied to create murine hybridomas[2]. However, the human B-cell lines were unstable, yielding only small amounts of the desired antibody, and few fully human mAbs entered clinical trials during the late 1980s.

Subsequent efforts concentrated on using genetic manipulation to produce human or humanlike monoclonal products. Chimeric mAbs, specifically human–murine hybrids (see "Monoclonal antibodies by design"), were described in several publications during 1984 (refs 3,4), and the first entered clinical trials in 1987. Researchers hoped that the human constant regions of the mAbs would not only

Year of approval	Commercial name	Active ingredient	Indication
1996	CEAScan	Arcitumomab	Diagnostic agent for carcinoma of the colon or rectum
1997	LeucoScan	Sulesomab	Diagnostic agent (location and extent of infection/inflammation of bones)
1998	Mabthera	Rituximab	Rheumatoid arthritis (RA)
	Simulect	Basiliximab	Prophylaxis of acute organ rejection in de novo allogeneic renal transplantation in adult and paediatric patients (1-17 years)
	Remicade	Infliximab	RA
1999	Zenapax	Daclizumab	Prophylaxis of acute organ rejection in de novo allogeneic renal transplantation
	Synagis	Pavilizumab	Prevention of serious lower respiratory tract disease by RSV
2000	Herceptin	Trastuzumab	Treatment of patients with metastatic breast cancer whose tumours overexpress HER2.
2001	MabCampath	Alentuzumab	Treatment of patients with B-cell chronic lymphocytic leukaemia
2003	Trudexa	Adalimumab	RA
	Humira	Adalimumab	RA, psoriasis
	Raptiva	Efalizumab	Chronic plaque psoriasis
2004	Erbitux	Cetuximab	Treatment of patients with EGFR-expressing, KRAS wt metastatic colorectal cancer
	Zevalin	Ibritumomab tiuxetan	Consolidation therapy after remission induction in previously untreated patients with follicular lymphoma
2005	Xolair	Omalizumab	Add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma
	Avastin	Bevacizumab	Treatment of patients with metastatic carcinoma of the colon or rectum, metastatic breast cancer, renal cell cancer, non small cell lung cancer
2006	Tysabri	Natalizumab	Single disease modifying therapy in highly active relapsing remitting multiple sclerosis

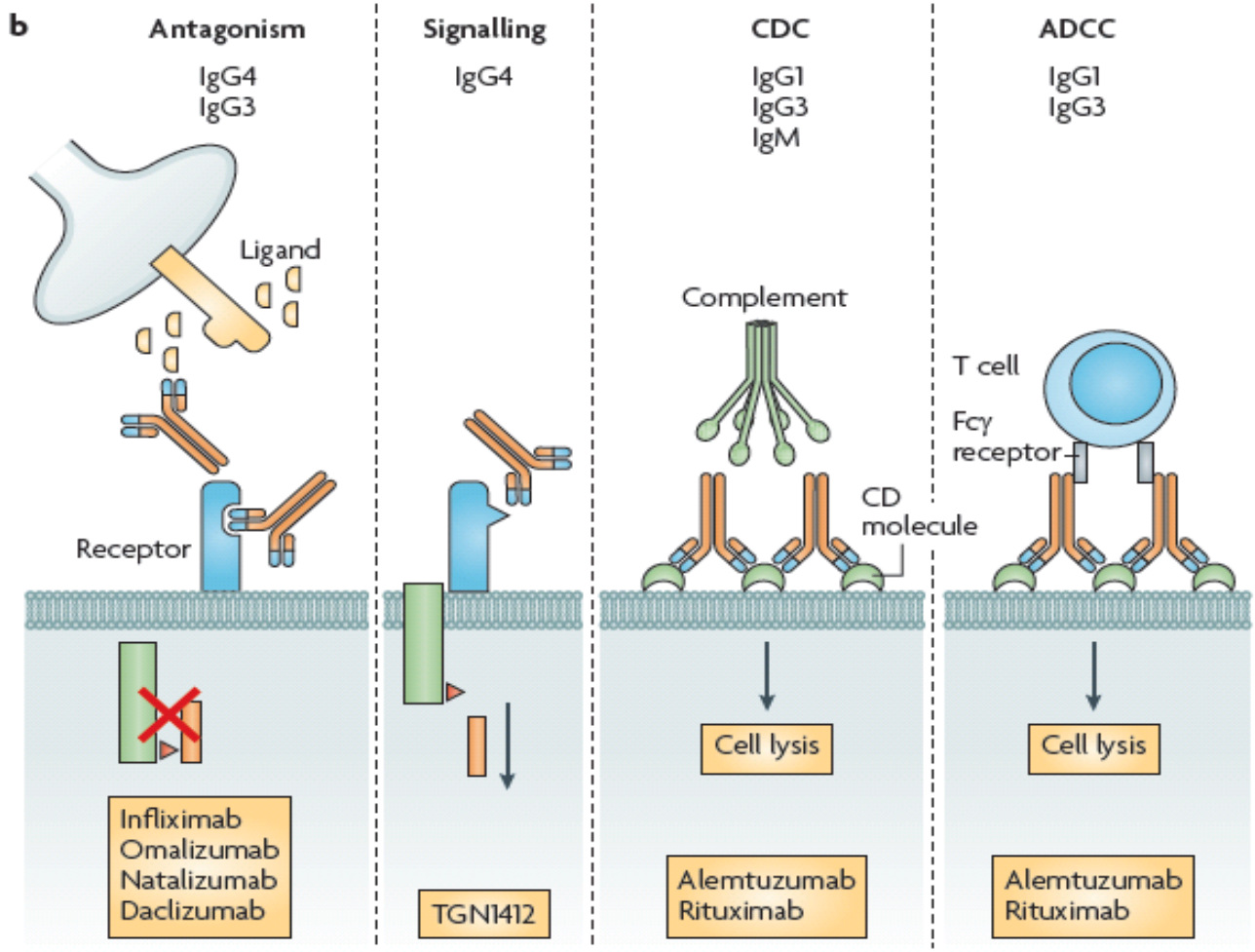
	Soliris	**Eculizumab**	Treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH)
2007	Vectibix	**Panitumumab**	Treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS
	Lucentis	**Ranibizumab**	Treatment of neovascular (wet) age-related macular degeneration (AMD)
	Removab	**Catumaxomab**	Intraperitoneal treatment of malignant ascites in patients with EpCAM positive carcinomas
	RoActemra	**Tocilizumab**	Rheumatoid arthritis in combination with MTX
	Stelara	**Ustekinumab**	Treatment of moderate to severe plaque psoriasis
	Cimzia	**Certolizumab pegol**	Rheumatoid arthritis in combination with MTX
2009	Simponi	**Golimumab**	Treatment of rheumatoid arthritis , psoriatic arthritis and ankylosing spondylitis
	Ilaris	**Canakinumab**	Treatment of adults, adolescents and children aged 4 years and older with Cryopyrin-Associated Periodic Syndromes (CAPS), including Muckle-Wells Syndrome (MWS), Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA), and severe forms of Familial Cold Autoinflammatory Syndrome (FCAS).
	Scintimun	**Besilesomab**	A radiopharmaceutical intended for use in scintigraphic imaging in adults with suspected osteomyelitis
	Prolia	**Denosumab**	Treatment of osteoporosis in postmenopausal women
2010	Arzerra	**Ofatumumab**	Arzerra is used to treat chronic lymphocytic leukaemia (CLL)
	Benlysta	**Belimumab**	Add-on therapy in adult patients with active autoantibody-positive systemic lupus erythematosus with a high degree of disease activity
2011	Yervoy	**Ipilimumab**	Treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy
	Xgeva	**Denosumab**	Prevention of skeletal-related events in adults with bone metastases from solid tumours

June 2012



Types of mAbs

Murine	Entirely murine amino acids	'o' = mouse e.g. muro**o**monab
Chimeric	Human constant (C) + murine variable (V) regions	'xi' = chimeric e.g. ritu**xi**mab
Humanized	Murine complementarity determining regions (CDRs)	'zu' = humanized e.g. alemtu**zu**mab
Human	Entirely human amino acids	'u' = human e.g. adalim**u**mab



Steps involved in obtaining an EU marketing authorisation

1. Submission of eligibility request

(At the earliest 18 months and at the latest 7 months in advance of submission).

2. Notification of intention to submit an application

(Approx. 7 months in advance of submission).

3. Appointment of rapporteurs

(Approx. 7 months in advance of submission).

4. Pre-submission meeting

(Approx. 7 months in advance of submission).

5. Submission of the application.

6. Scientific evaluation

(210 days of assessment).

7. CHMP scientific opinion.

8. European Commission decision on the marketing authorisation.

Useful information

On the European Medicines Agency website: Regulatory > Human Medicines > Pre-authorisation

EMA pre-submission procedural advice for users of the centralised procedure (EMA/339324/2007).

Regulation (EC) No 726/2004.

The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 4 on 'Centralised procedure'.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Further information

European Medicines Agency

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Canary Wharf
London E14 4HB
United Kingdom

Telephone +44 (0)20 7418 8400
Facsimile +44 (0)20 7418 8416
E-mail info@ema.europa.eu
Website www.ema.europa.eu

Applying for EU marketing authorisation

For medicinal products for human use

An agency of the European Union

Which products *must* be centrally authorised?

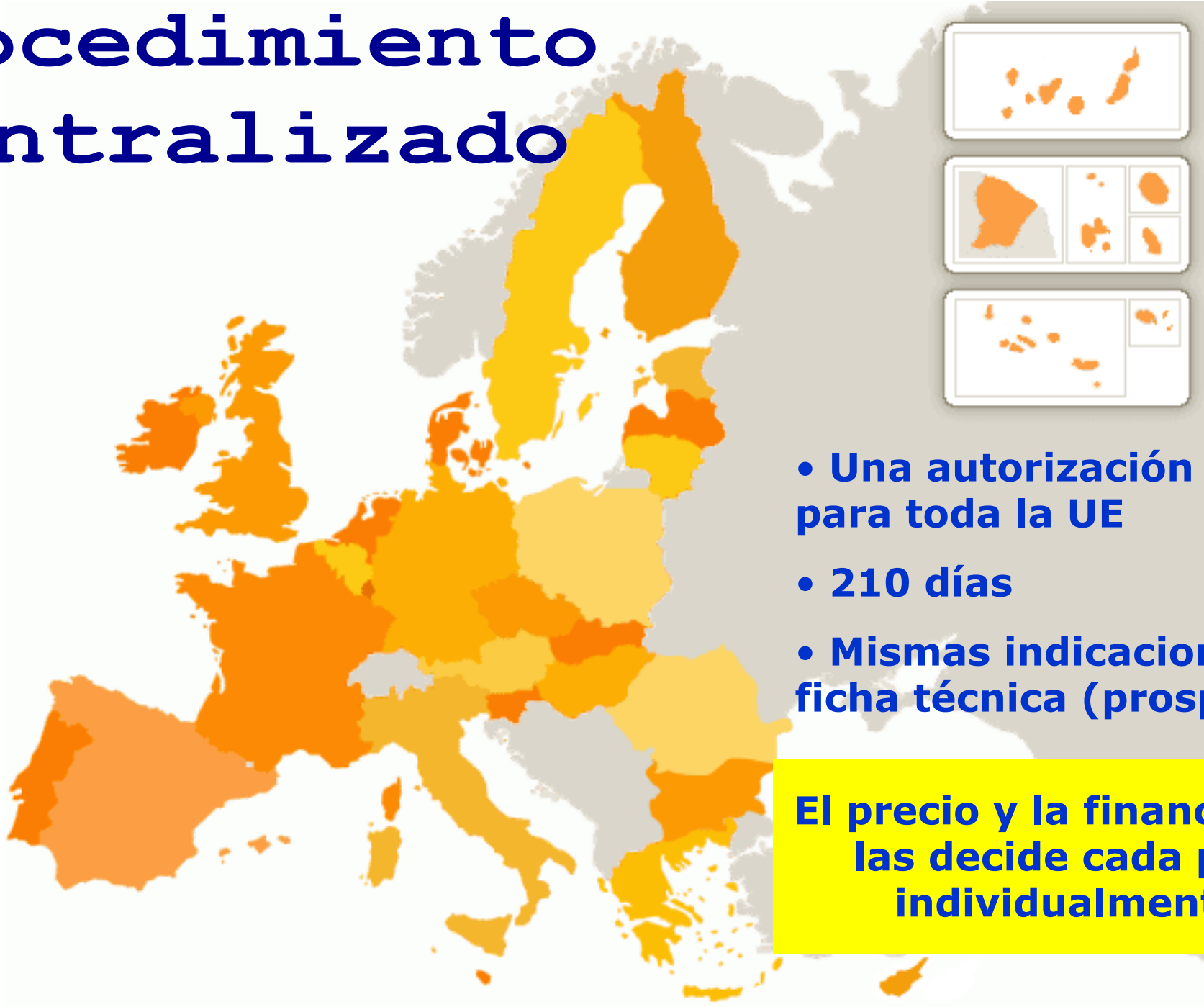
All human medicines derived from biotechnology and other high-tech processes must be evaluated by the Agency via the centralised procedure. The same applies to all advanced-therapy medicines and medicinal products containing new active substances intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases.

Which products may *optionally* be centrally authorised?

For medicines that do not fall under any of the abovementioned categories, companies can submit an application to the Agency, provided the medicine is a new active substance, constitutes a significant therapeutic, scientific or technical innovation, or is in any other respect in the interest of patients at EU level.

Also, generics of centrally authorised products and applications for certain medicinal products for paediatric use may be authorised in this way.

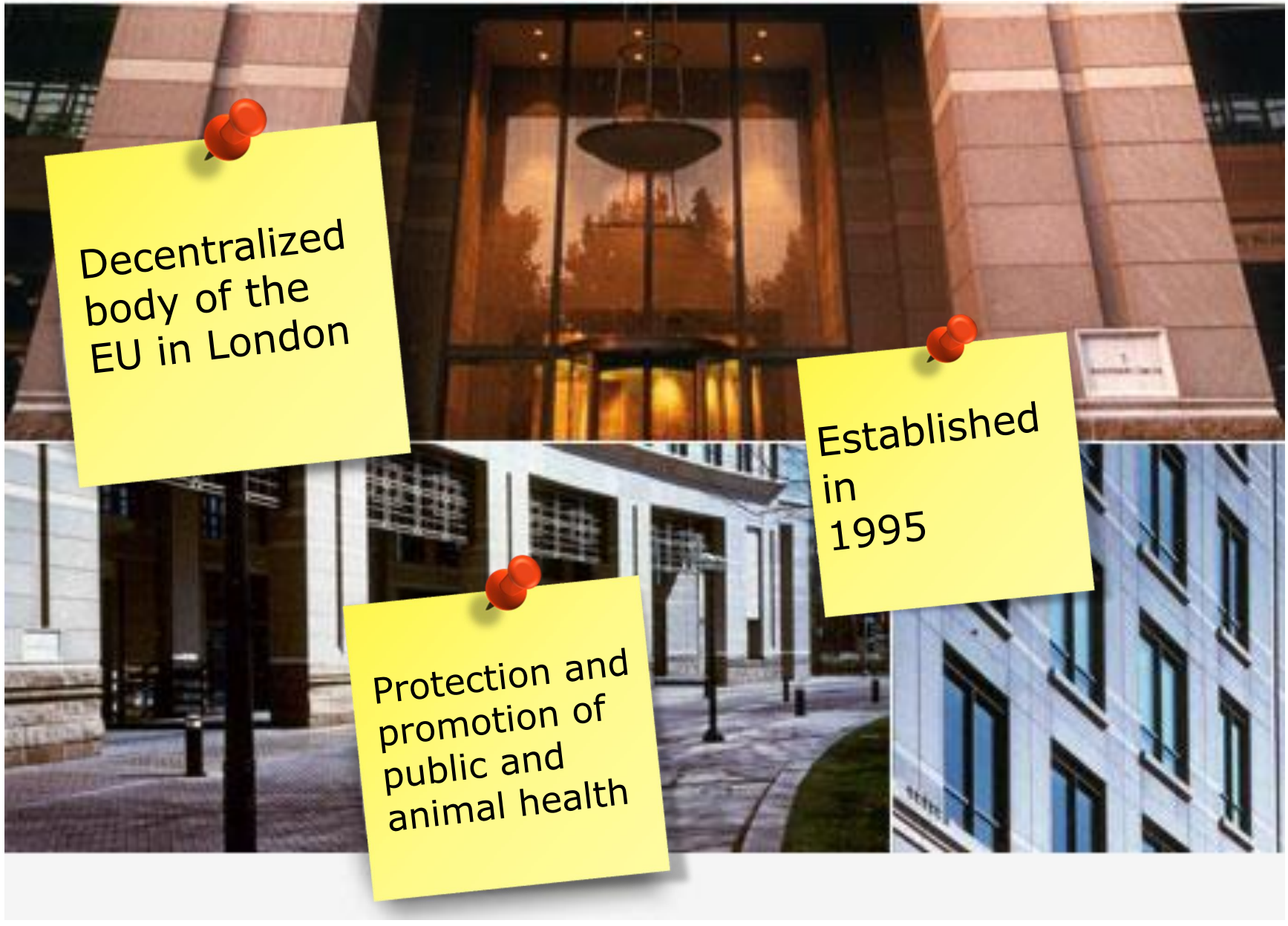
procedimiento centralizado



- **Una autorización única para toda la UE**
- **210 días**
- **Mismas indicaciones y ficha técnica (prospecto)**

El precio y la financiación las decide cada país individualmente

european medicines agency



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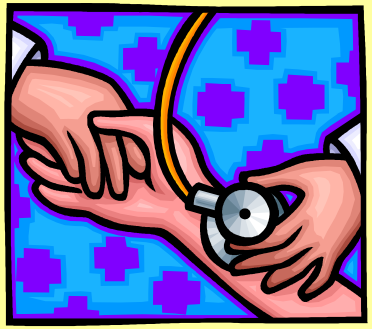
SCIENTIFIC COMMITTEES

CHMP



Human

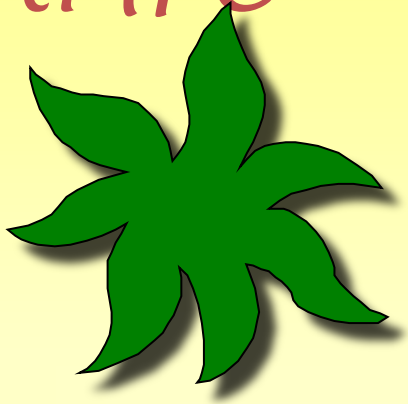
CVMP

Vet

COMP

Orphan

HMPC



Herbal

cat

prac

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CHMP

Human Meds

FINAL opinion on medicines for human use

CHMP

- Chair & Vice-Chair
- **1** scientific expert **member** nominated by each MS (+**1 alternate**) **- 28**
- **1** scientific expert **member** from NO and ICE (+**1 alternate**) (observers)
- **5 co-opted members** (experts in specific areas of interest for the CHMP)

Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 21-24 July 2014

News

25/07/2014

Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 21-24 July 2014

This page provides an overview of the opinions adopted at the July 2014 meeting of the Committee for Medicinal Products for Human Use (CHMP) and other important outcomes.

Five new medicines recommended for approval

The CHMP has recommended granting marketing authorisations for two new medicines for the treatment of various rare cancers of the blood, **Imbruvica** (ibrutinib) and **Zydelig** (idelalisib). Please see the press release in the grid below for more information.

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.

The generic medicine **Busulfan Fresenius Kabi** (busulfan) was also recommended for authorisation for conditioning treatment prior to conventional haematopoietic progenitor cell transplantation.

Seven recommendations on extensions of therapeutic indications

The Committee recommended extensions of indications for **Baraclude**, **Busilvex**, **Ecalta**, **Humira**, **Ozurdex**, **RoActemra** and **Xgeva**.

Outcome of review on emergency contraceptives

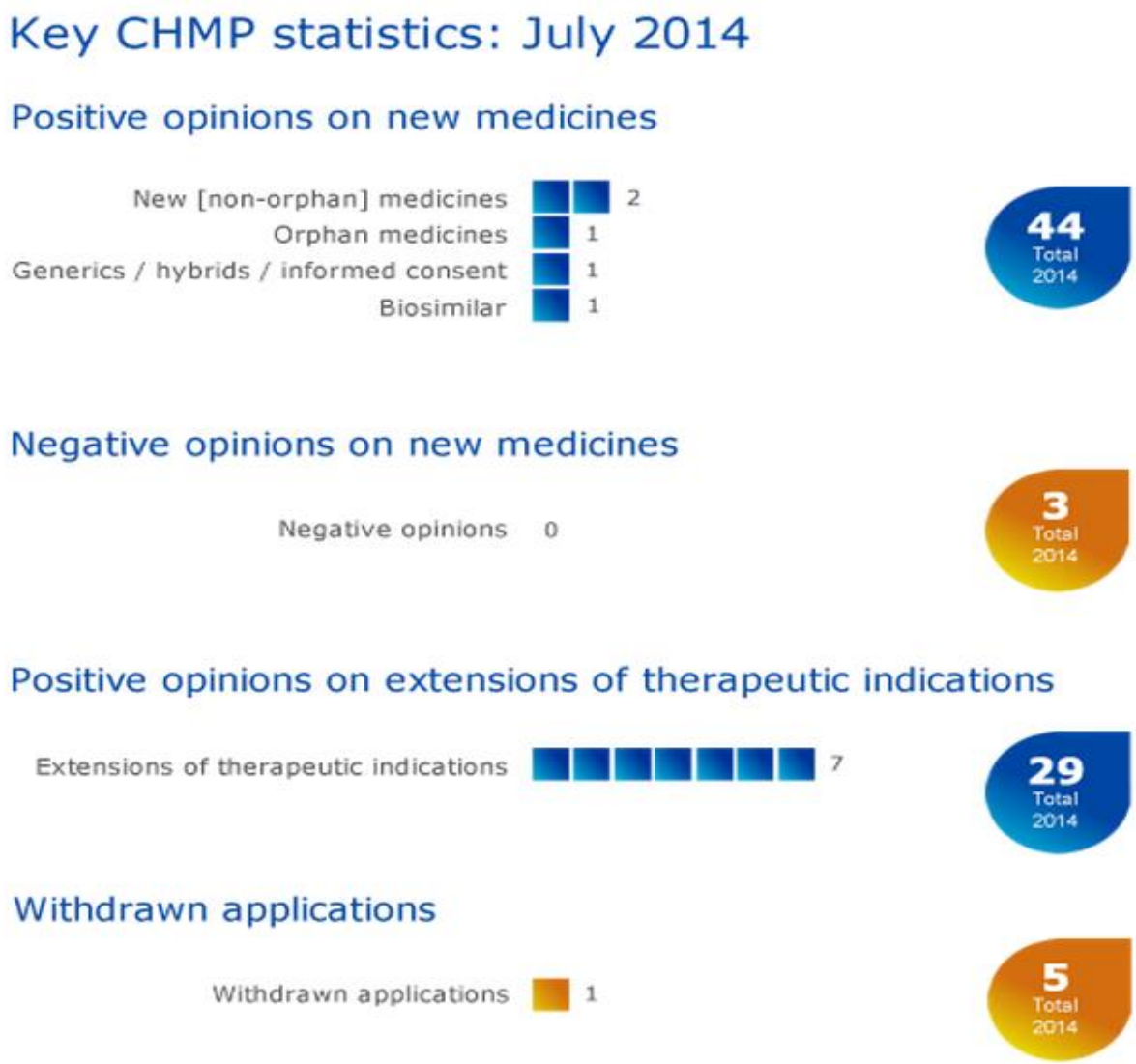
The CHMP has concluded its review of emergency contraceptives containing levonorgestrel and ulipristal acetate.

Related information

- Baraclude: EPAR
- Humira: EPAR
- Busilvex: EPAR
- RoActemra: EPAR
- Xgeva: EPAR
- Ecalta: EPAR
- Ozurdex: EPAR
- Ecalta: Pending EC decision
- Busulfan Fresenius Kabi: Pending EC decision
- Busilvex: Pending EC decision
- Zydelig: Pending EC decision
- Accofil: Pending EC decision
- Baraclude: Pending EC decision
- Xultophy: Pending EC decision
- Xgeva: Pending EC decision
- RoActemra: Pending EC decision
- Ozurdex: Pending EC decision
- Imbruvica: Pending EC decision
- Neofordex: Withdrawn application
- Emergency contraceptives
- European Medicines Agency recommends approval of two new treatment options for rare cancers (25/07/2014)
- Levonorgestrel and ulipristal

CHMP statistics

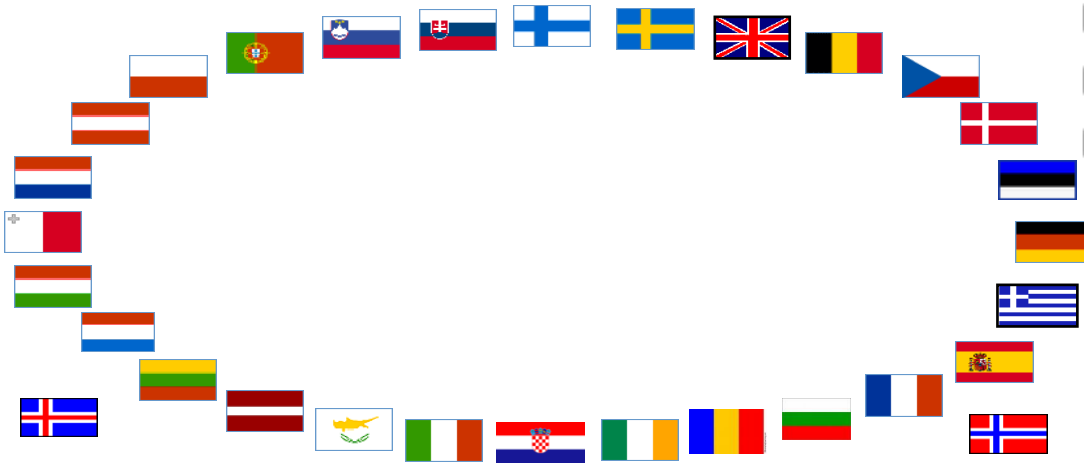
Key figures from the July 2014 CHMP meeting are represented in the graphic below.



* These figures include the outcomes of re-examination procedures

Source: European Medicines Agency

CHMP



+

5 coopted members

Standing working parties

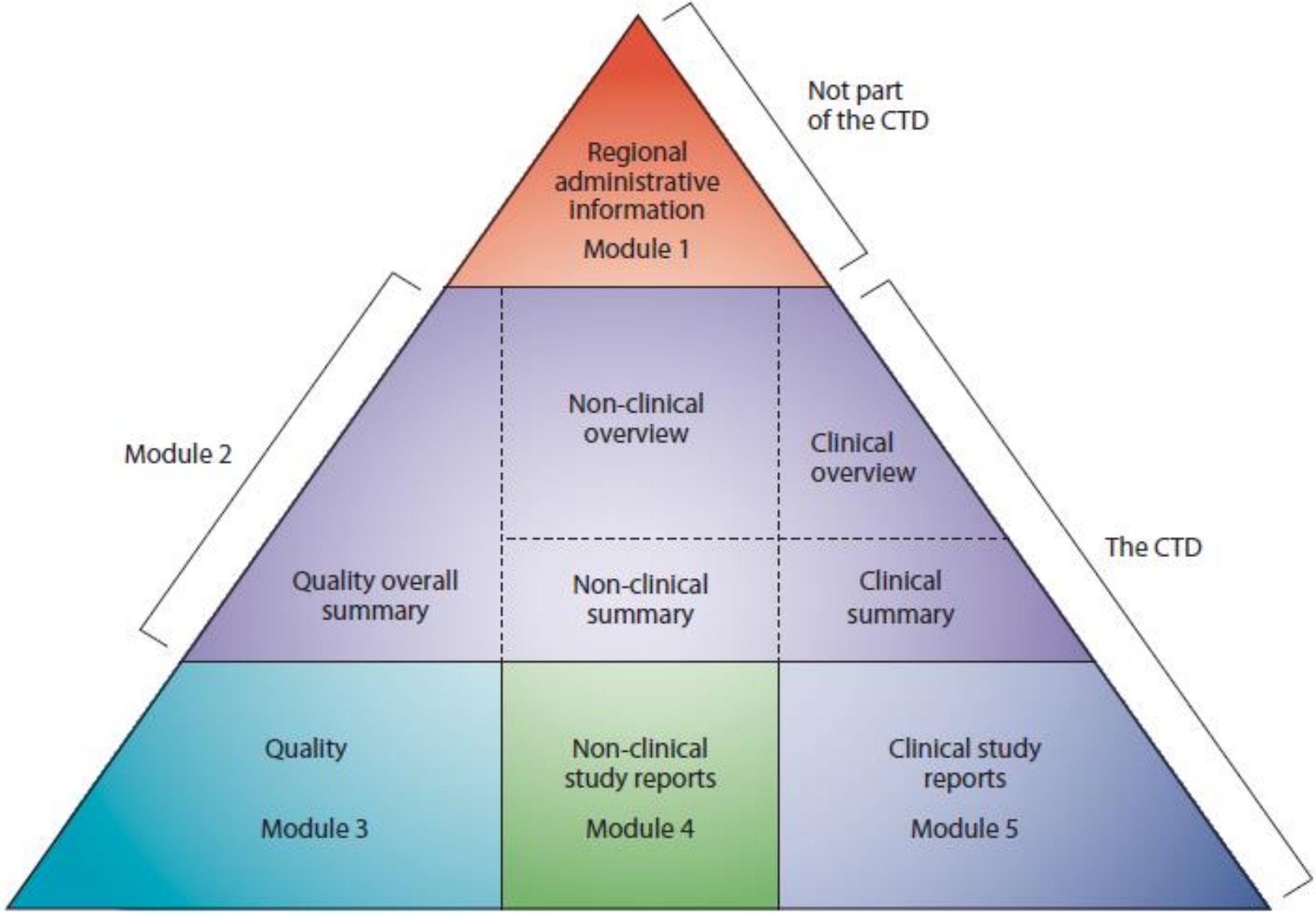
The current CHMP **standing working parties** are:

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

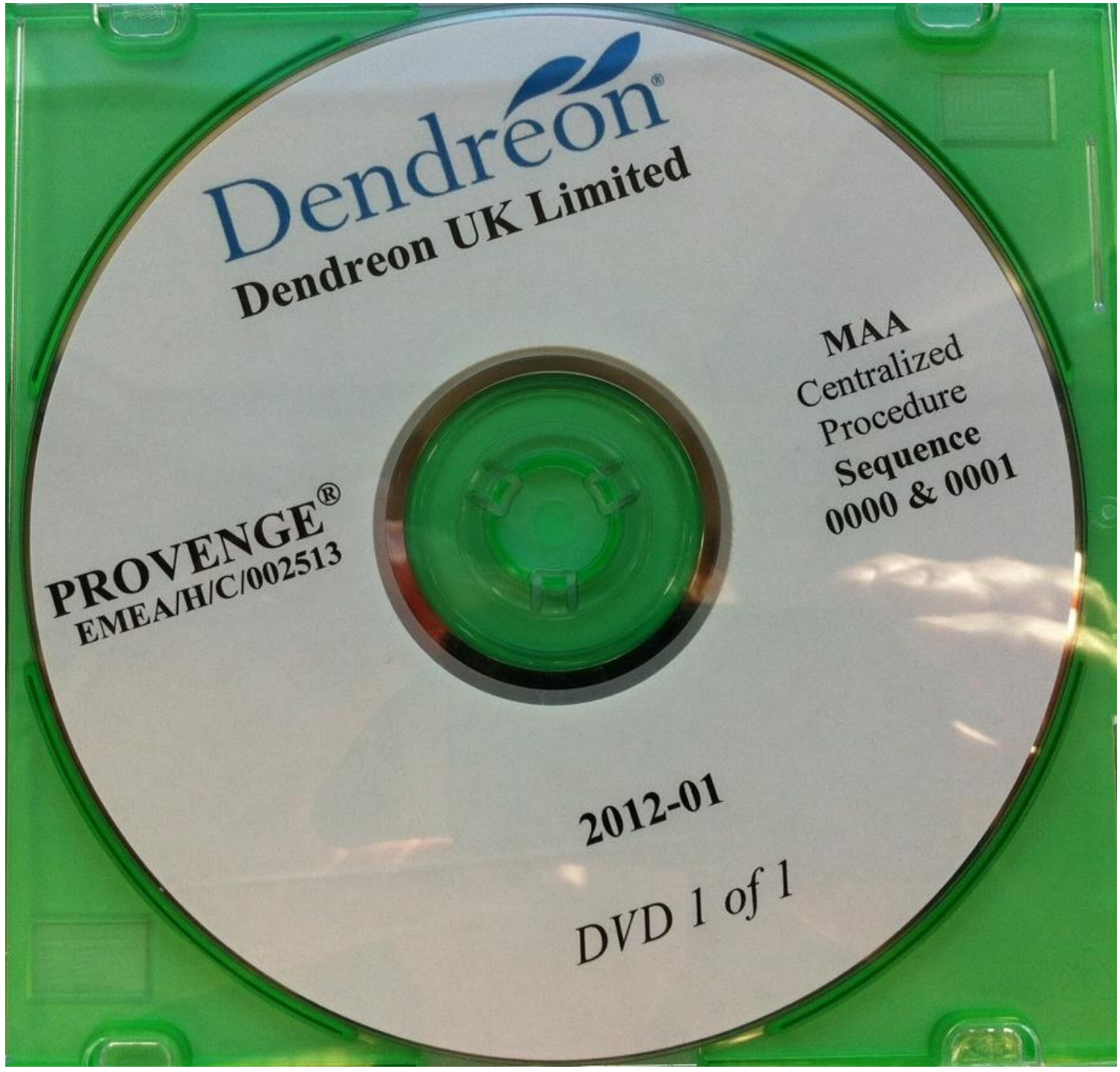
The current CHMP temporary working parties are:

- 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

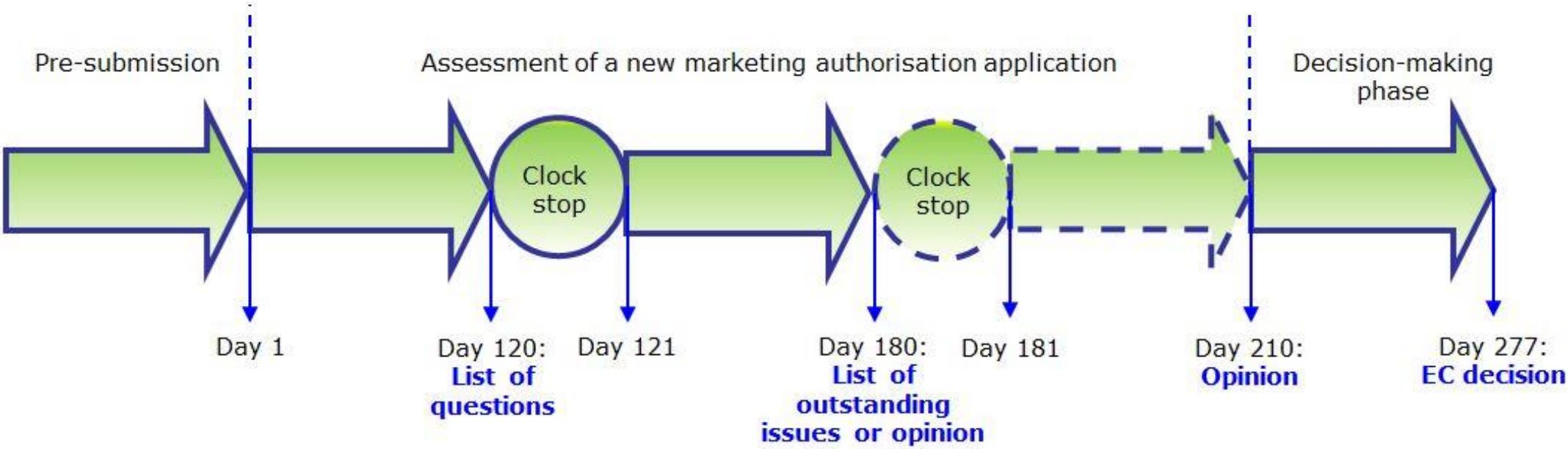

IN GOD WE TRUST
ONE



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.


Dendreon
Dendreon UK Limited
MAA
Centralized
Procedure
Sequence
0000 & 0001
PROVENGE®
EMEA/H/C/002513
2012-01
DVD 1 of 1

Centralised Procedure



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

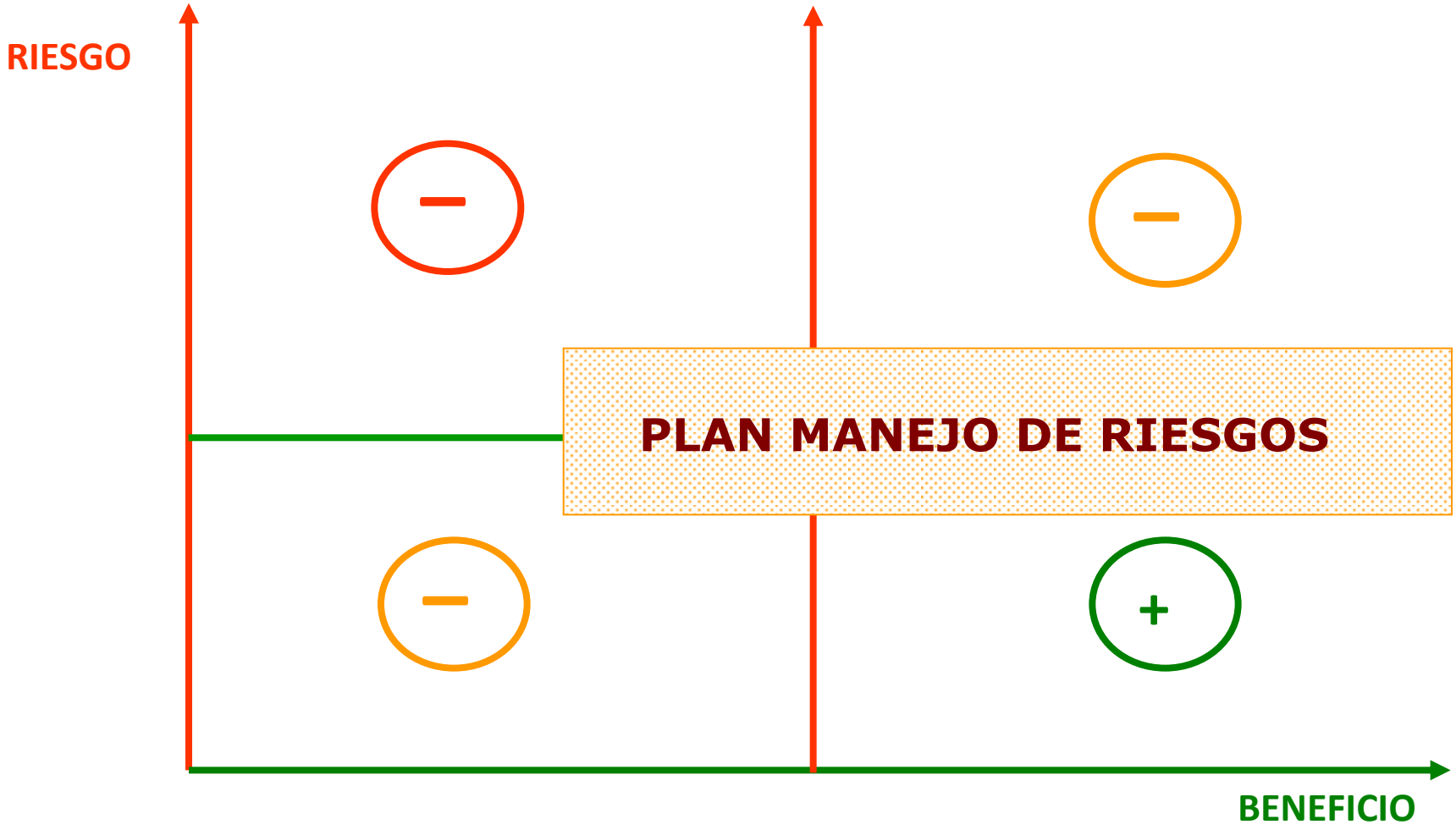
Importance of favourable and unfavourable effects

Benefit-risk balance

Discussion on the benefit-risk assessment

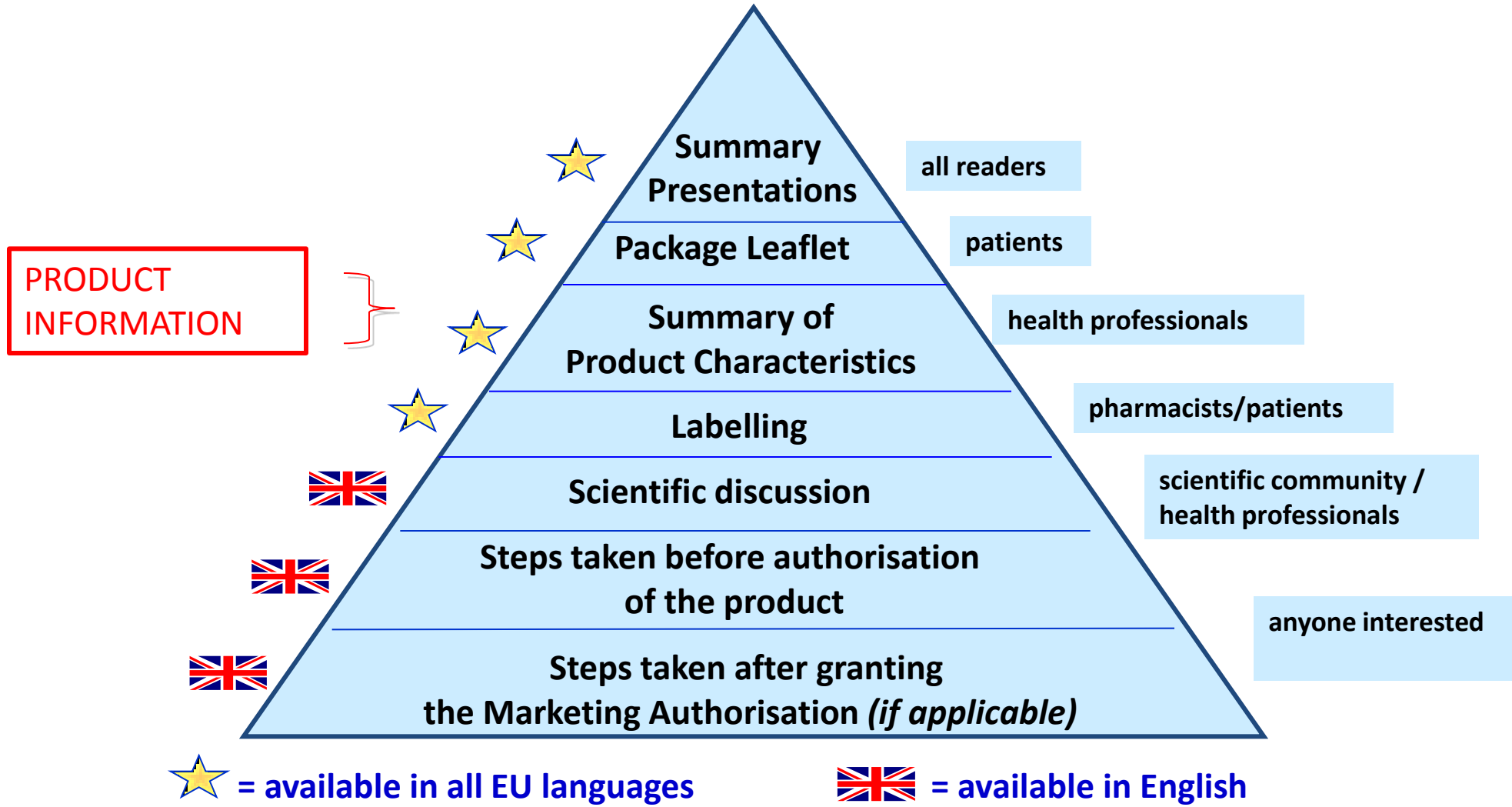
5.1. Conclusions

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


RIESGO
PLAN MANEJO DE RIESGOS
BENEFICIO

EPAR

European Public Assessment Report



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SCIENCE MEDICINES HEALTH

Text size: A A A

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- Patient safety
- Pending EC decisions
- Withdrawn applications
- Paediatrics
- Rare disease designations
- Med outside the EU
- Veterinary medicines
- Herbal medicines for human use

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General information to the public

Email Print Help Share

About | **Authorisation details** | **Product information** | **Assessment history**

« Previous tab

Changes since initial authorisation of medicine

Name, INN, therapeutic area, MAH

	Language	First published	Last updated
Levemir : EPAR - Procedural steps taken and scientific information after authorisation	(English only)	15/06/2009	18/05/2011

Initial Marketing auth

SmPC, Labelling, Package leaflet, Presentations, Manufacturers (MAH, AS), Conditions to the MA

Name		
Levemir : EPAR - Scientific Discussion	(English only)	15/08/2006
Levemir : EPAR - Procedural steps taken before authorisation	(English only)	15/08/2006

AUTHORISED
This medicine is approved for use in the European Union

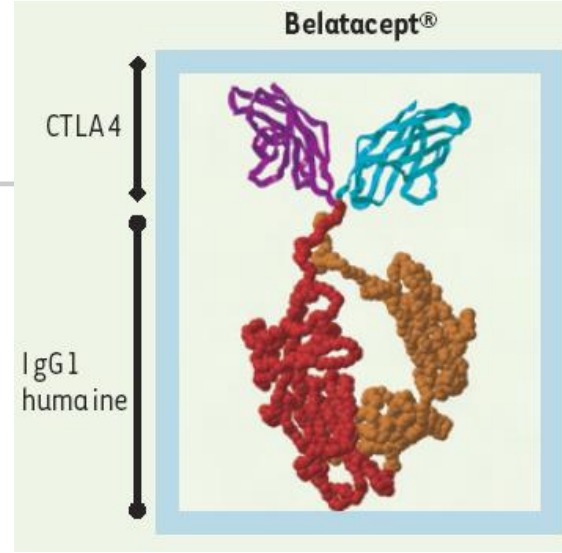
Related information

- Levemir: Paediatric Investigation Plan


"WHAT'S UP, DOC?"

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Nulojix



On 14 April 2011the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Nulojix 250 mg powder for concentrate for solution for infusion, intended for the prophylaxis of graft rejection in adults receiving a renal transplant. The applicant for this medicinal product is Bristol-Myers Squibb. 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 Nulojix is belatacept, a selective immunosuppressants (ATC code: L04AA28).Belatacept binds to CD80 and CD86 on antigen presenting cells. As a result, belatacept blocks CD28 mediated co-stimulation of T cells inhibiting their activation, thus leading to immunosuppression.

The benefits of Nulojix are its ability to be non-inferior to ciclosporin for patient and graft survival at 12 months in both low and high risk populations, with positive effects on renal function. Results were sustained through 36 months. A superior effect on renal function was only demonstrated in the low risk population, while more episodes of acute rejection occurred with belatacept treatment compared to ciclosporin in this population.

FRESH FROM THE PIPELINE

Belimumab

Iñaki Sanz, Uma Yasothan and Peter Kirkpatrick

In March 2011, belimumab (Benlysta; Human Genome Sciences/GlaxoSmithKline), a human monoclonal antibody that is specific for the cytokine B lymphocyte stimulator, was approved by the US Food and Drug Administration (FDA) for the treatment of systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a complex autoimmune disease that can affect multiple organ systems, including the kidneys, the skin, the lungs, the heart and the central nervous system (CNS)[1]. It is characterized by a recurring and variable pattern of disease flare and remission, and its presentation can range from mild symptoms

Drug properties

Belimumab is a human immunoglobulin G1λ monoclonal antibody (mAb) that is specific for soluble human BLYS[5–7]. It blocks the binding of soluble BLYS to its receptors on B cells, thereby inhibiting the survival of B cells — including autoreactive B cells — and reducing the differentiation of B cells into immunoglobulin-producing plasma cells[5–7].

Clinical data

The safety and effectiveness of belimumab (administered as an intravenous infusion) were assessed in three randomized, double-blind, placebo-controlled trials that involved 2,133 patients with SLE (diagnosis of

Informed by this analysis, two further randomized, double-blind, placebo-controlled trials in patients with active SLE disease (defined as a SELENA-SLEDAI score of ≥6) and with positive autoantibody test results at screening were conducted[7]. The two trials were similar in design, except one (involving 865 patients) was 52 weeks in duration, whereas the other (involving 819 patients) was 76 weeks in duration[7]. More than 50% of patients in these two trials had three or more organ systems with active SLE disease at baseline, and most patients (>70%) were receiving two or more classes of SLE medications[7]. The patients were randomly assigned to receive belimumab (1 mg or 10 mg per kg) or placebo on days 0, 14 and 28, and then every 28 days for 48 weeks in the 52-week

Box 1 | **Market for systemic lupus erythematosus**

Analysing the market for systemic lupus erythematosus (SLE) is Uma Yasothan, IMS Health, London, UK.

In March 2011, the monoclonal antibody belimumab (Benlysta; Human Genome Sciences/ GlaxoSmithKline) became the first new drug to be approved by the US FDA for SLE in 50 years. Belimumab has been launched in the United States at a price of US$2,806 per infusion and is anticipated to bring in revenues of $35,000 per year per patient with SLE[9]. There are no particular challenges associated with its reimbursement and the initial insurance coverage appears to be broad. GlaxoSmithKline and Human Genome Sciences have also set up the 'Benlysta Gateway', a support programme to maximize access for eligible patients. Belimumab has been submitted for regulatory approval in Europe and is in clinical trials for other indications (primarily Sjogren's syndrome and kidney transplantation). A subcutaneous form of the drug is also in advanced development. Analysts' expectations for 2011 sales are ~$85 million[9], with peak year sales of ~$3 billion in 2018 (REF. 10).

Current sales of the drug are modest, at 70 million pounds ($106 million) in 2012, but GSK hopes it will become a major seller.

(http://www.reuters.com/article/2013/04/03/glaxosmithkline-benlysta-idUSL5N0CQ2NN20130403)

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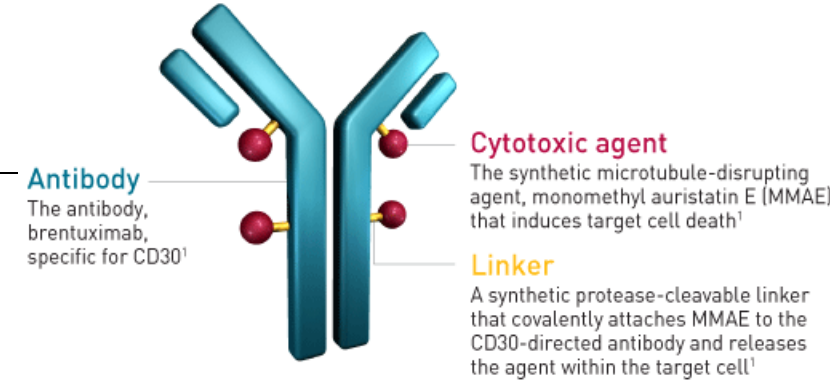
19 July 2012
EMA/CHMP/471107/2012
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (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 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

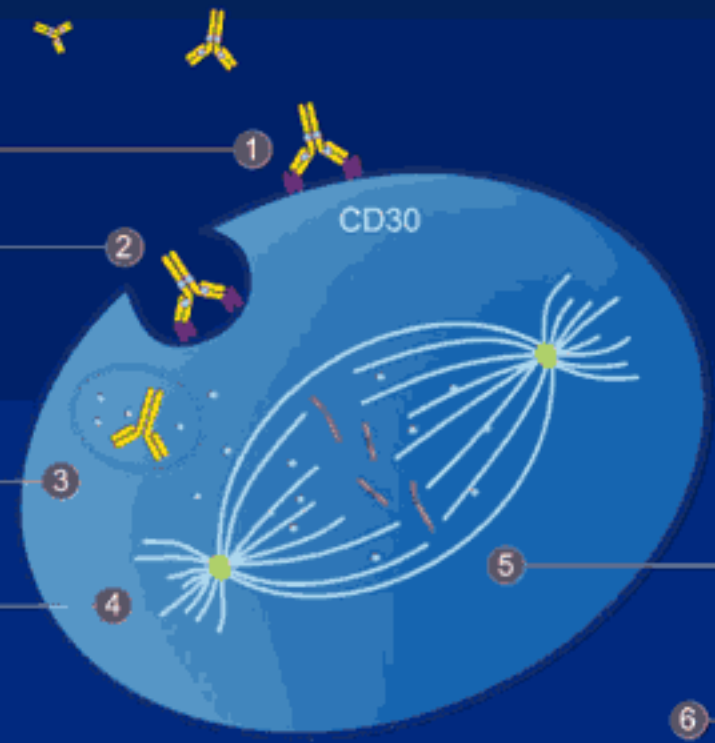
Brentuximab vedotin (SGN-35) ADC
monomethyl auristatin E (MMAE), potent antitubulin agent
protease-cleavable linker
anti-CD30 monoclonal antibody

ADC binds to CD30

ADC-CD30 complex traffics to lysosome

MMAE is released

MMAE disrupts microtubule network



G2/M cell cycle arrest

Apoptosis

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

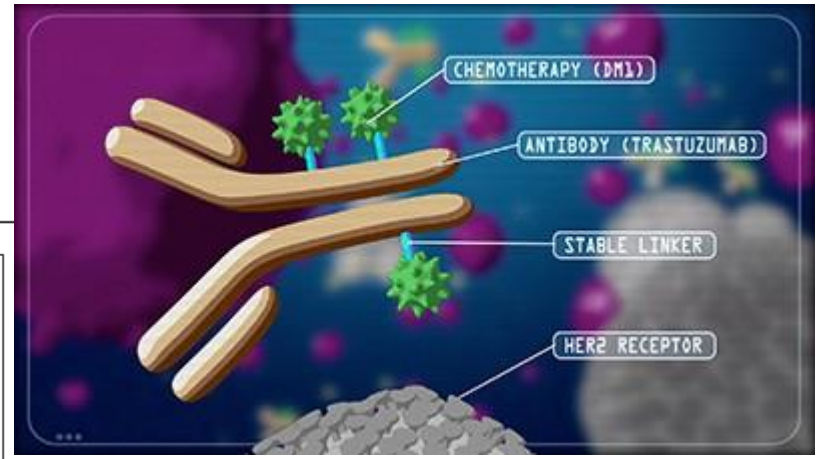
Granting a marketing authorisation to **Xultophy** (insulin degludec/liraglutide) for the treatment of diabetes mellitus has also been recommended.

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

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

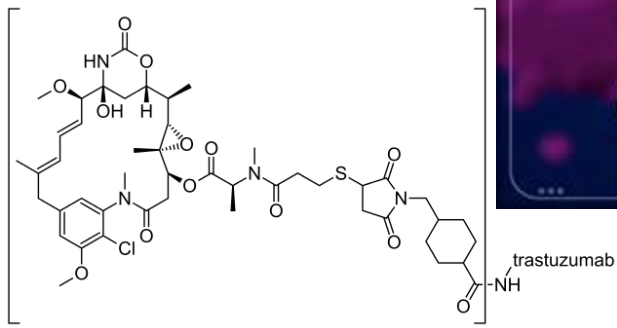
EMA/748315/2013
EMEA/H/C/002389

EPAR summary for the public



Kadcyla

trastuzumab emtansine



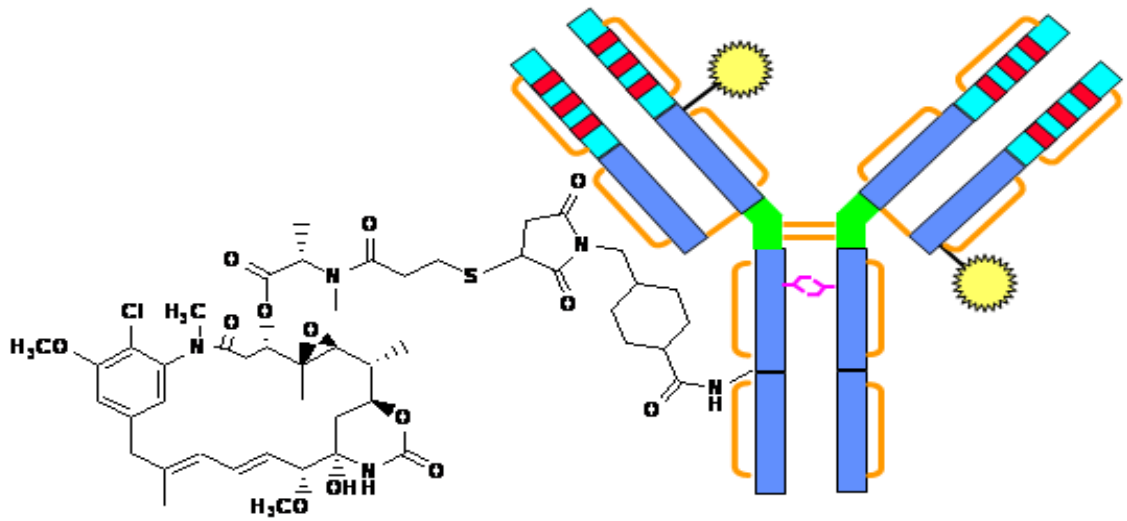
This is a summary of the European public assessment report (EPAR) for Kadcyla. It explains how the Agency assessed the medicine to recommend its authorisation in the EU and its conditions of use. It is not intended to provide practical advice on how to use Kadcyla.

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).

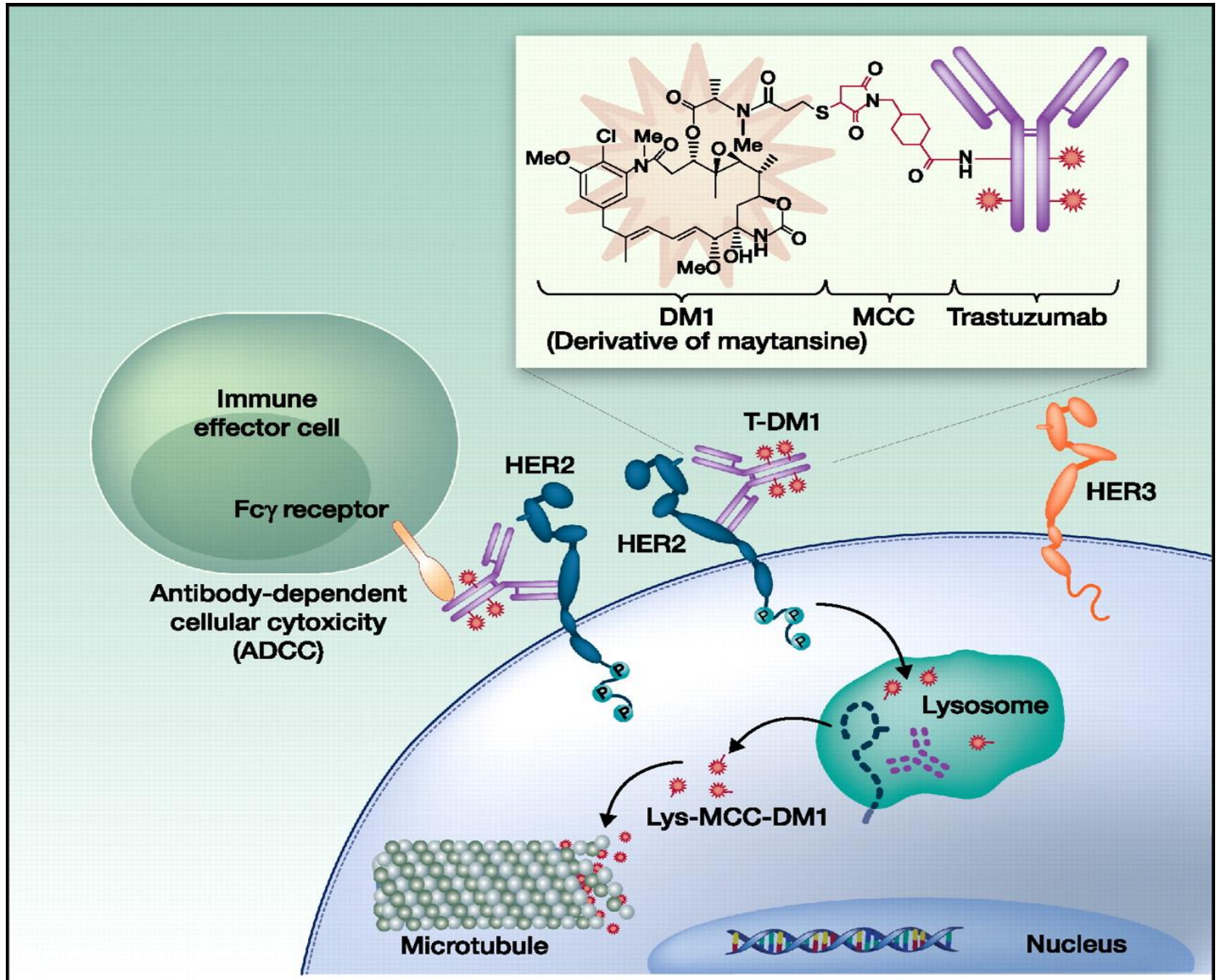
Kadcyla can only be used when the cancer has been shown to 'overexpress HER2': this means that the cancer cell produces on its surface large quantities of a protein which stimulates the growth of the cancer cell and is called HER2 (human epidermal growth factor).



DM1 = (3 to 4 per IgG)

Linker -thioether-

Trastuzumab (HzIgG1) -LysNH_2 (random)



22 May 2014
EMA/CHMP/280012/2014
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

Gazyvaro

obinutuzumab

On 22 May 2014, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Gazyvaro 1,000 mg concentrate for solution for infusion intended for the treatment in combination with chlorambucil of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy. Gazyvaro was designated as an orphan medicinal product on 10 October 2012. The applicant for this medicinal product is Roche Registration 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.

The active substance of Gazyvaro is obinutuzumab, a recombinant monoclonal antibody (L01XC15) targeting the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes. In nonclinical studies, obinutuzumab induces direct cell death and mediates antibody dependent cellular cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP).

The benefits with Gazyvaro used in combination with chlorambucil (Clb) are its ability to delay the progression of disease compared to Clb alone or rituximab in combination with Clb. The most common side effects are infusion-related reactions (IRRs) which occurred in the majority of patients during the first cycle, neutropenia and infections.

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

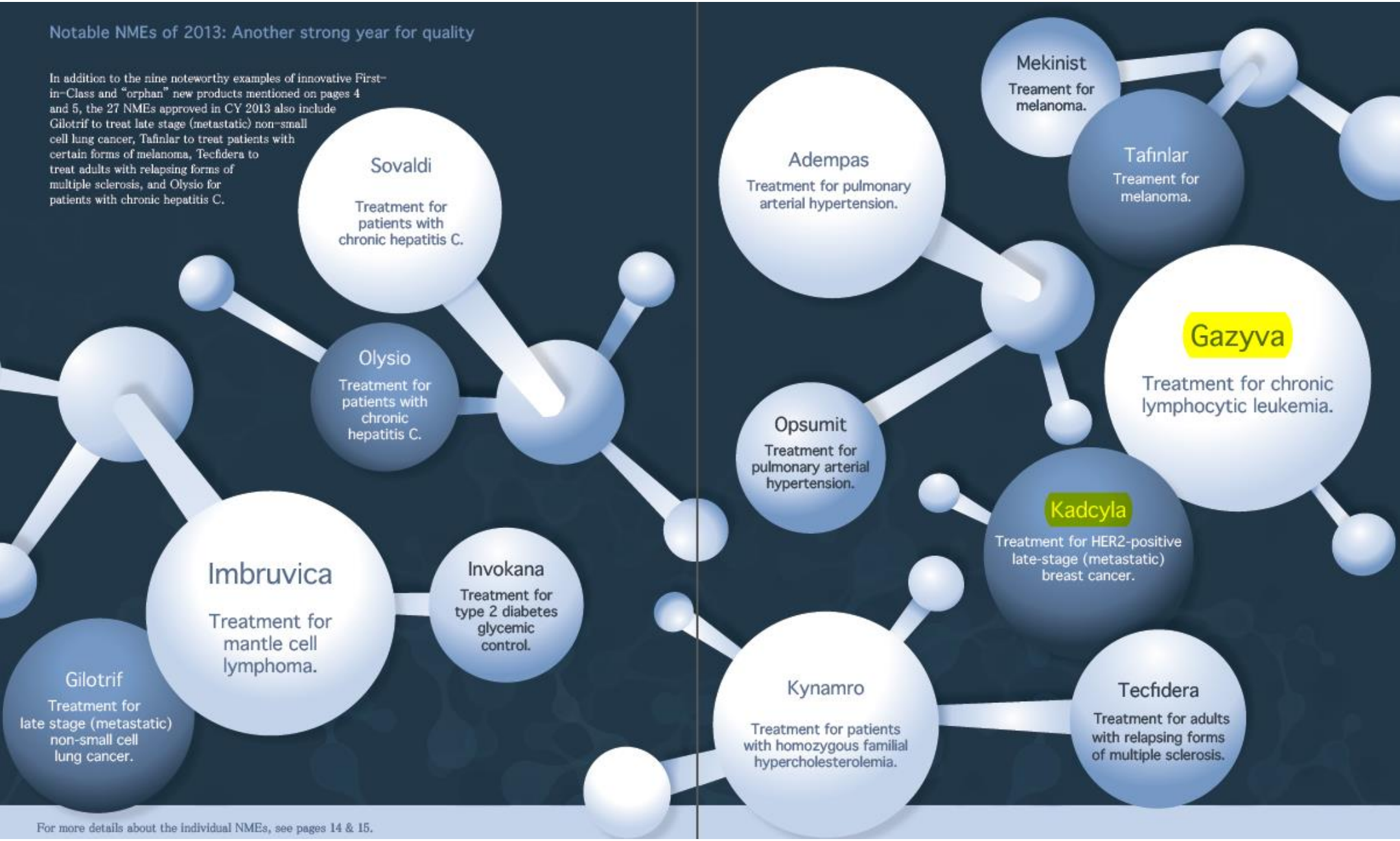
Innovation drives progress. When it comes to innovation in the development of new drugs and therapeutic biological products, FDA's Center for Drug Evaluation and Research (CDER) supports the pharmaceutical industry at every step of the process. With its understanding of the science used to create new 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.

Billion dollar babies—biotech drugs as blockbusters

Last year marked the first time that erythropoietins were not the top-selling biotech drugs. Stacy Lawrence looks at the biopharmaceuticals that have usurped them.

Like big pharma, the biotech industry is lucky to produce a few treatments a year that will achieve annual sales of more than $1 billion. Last year just happened to be one of those fruitful years.

After a complete dearth of approved blockbuster prospects in 2005, two biotech drugs approved by the US Food and Drug Administration (FDA) in 2006 are expected to achieve blockbuster status in the next few years—HIV cocktail treatment Atripla (efavirenz, emtricitabine and tenofovir), marketed jointly by Gilead of San Francisco and Bristol-Myers Squibb of New York and the human papilloma virus (HPV) vaccine, Gardasil, from MedImmune of Gaithersburg, Maryland and Merck of Whitehouse Station, New Jersey.

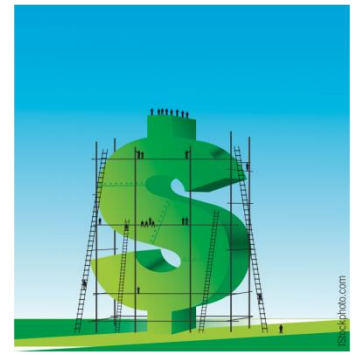
In addition, last year three biotech drugs that were approved in 2004 brought in more than $1 billion each: two monoclonal antibodies (mAbs) used in cancer treatment, S. San Francisco–based Genentech's Avastin (bevacizumab), and New York-based ImClone System's Erbitux (cetuximab) and another Gilead HIV cocktail, Truvada (emtricitabine and tenofovir), the latter two achieving blockbuster status for the first time (**Table 1** and **Supplementary Table 1** online).

Despite some predictions to the contrary, the blockbuster is not going away anytime soon in the drug industry. In fact, since the beginning of this decade the number of blockbuster drugs has tripled. And the good news for the industry is that biotech products are figuring more prominently into this picture, currently accounting for about one-sixth of blockbusters.

Biotech hits 'the big time'

In the drug industry as a whole, 101 drugs each brought in more than $1 billion in worldwide sales in 2006, according to Tim Kelly, senior principal at IMS Health in Norwalk, Connecticut. Of these, 18 were biotech drugs As an industry, biotech will account for 24% of the 2007 pharmaceutical market sales growth of $35 billion, according to IMS Health.

Even as the total number of $1 billion–plus drugs has grown, biotech has more than doubled its share of blockbusters over the past six years. In 2000, there were a total of 36 blockbuster drugs—only three (8%) of which were biotech products.



Biotechs can take several avenues to a blockbuster drug.

Biotech represents an even larger share of the 'super' blockbusters—drugs with sales exceeding $2 billion. In 2006, there were 36 drugs that fell into this category, eight (22%) of which were biotech products according to IMS.

Adding a couple of blockbusters a year is a significant feat for biotech, particularly because only a handful of drugs launch annually. In 2006, there were about eight new biotech drugs. This year, expect ten new biotech drugs. In 2008, Kelly anticipates the number of biotech products will be in the teens.

Indeed, biotech may have an edge when it comes to the blockbuster. Although the high cost of biotech drugs may be at odds with the US political drive to curb drug costs, biotech innovations have won support for addressing unmet needs for serious conditions. Although the argument that high R&D and manufacturing costs justify the high prices may not win everyone over as in the past, producing highly efficacious products for unmet medical needs is likely to stay a winning strategy.

For pharma, the traditional model for a giant blockbuster has been to aim for a treatment that is not too specifically targeted, but can be prescribed at a lower price to a large number of patients for a fairly common condition. But the days of the blockbuster driven by a crowd of sales and marketing people are over, according to Mark Belsey, an analyst at the research group Datamonitor of London. He cites Pfizer's cholesterol-lowering drug Lipitor (atorvastatin), which made $12 billion in 2005, as an example of a traditional biopharmaceutical blockbuster that is widely marketed and driven by an enormous sales force. "I think in the future that R&D is going to dominate, not marketing," concludes Belsey, "and it costs less than sales people."

"The industry has realized that it needs to shift the weight of its drug development much more toward R&D," Belsey adds. But that's not what it takes to produce blockbuster drugs. "The level of unmet need, competition, all that governs whether a drug turns into a blockbuster," he says.

Early blockbusters

Most biotech blockbusters today are oncology or oncology-supporting products, like industry mainstay erythropoietin (Epogen or Procrit recombinant human erythropoietin, marketed by Amgen of Thousand Oaks, California, and Johnson & Johnson's Ortho Biotech of Bridgewater, New Jersey, respectively, also manufactured and sold in Europe by Ortho as Eprex) and up-and-comer Avastin (bevacizumab, for metastatic colon cancer), but early blockbusters were mainly protein replacement therapies. The FDA approved the first biotech blockbusters, Epogen and Neupogen (filgrastim, Amgen's recombinant granulocyte-colony stimulating factor prescribed for neutropenia) in the 1980s and early 1990s. These revenue cornerstones built Amgen into the first sizeable biotech company. But the science was relatively simple by today's standards, based on the re-creation of existing substances.

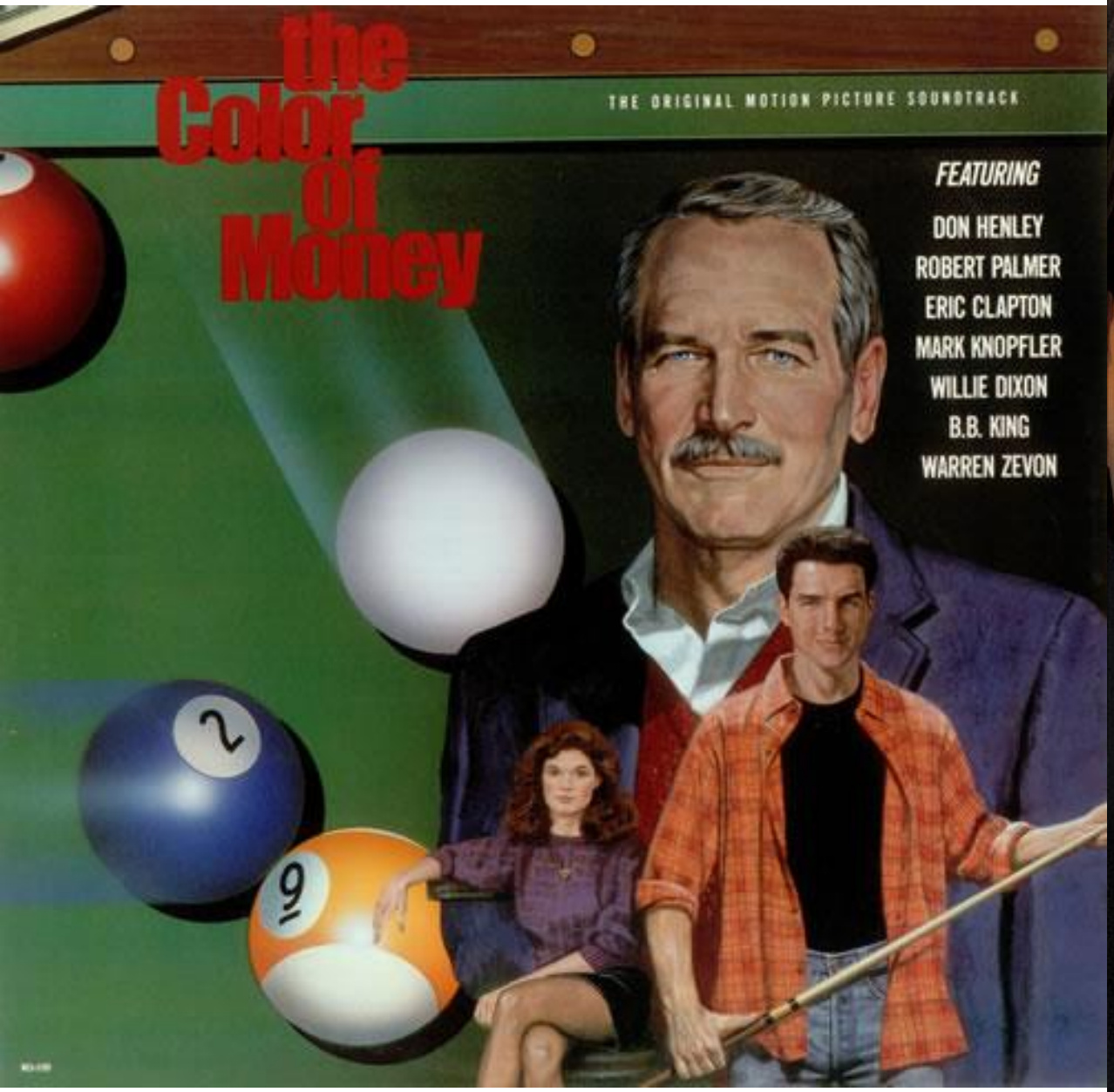
These products are becoming obsolete as second-generation versions have come to market in the past few years, and sales have slipped as the products have started to age. That's not a worry for Amgen, whose second-generation versions of these industry staples, Aranesp and Neulasta (darbepoetin alfa and PEG-filgrastim, respectively, both long-acting forms of their predecessors) were approved early this decade and are now largely cannibalizing revenues of first-generation erythropoietins.

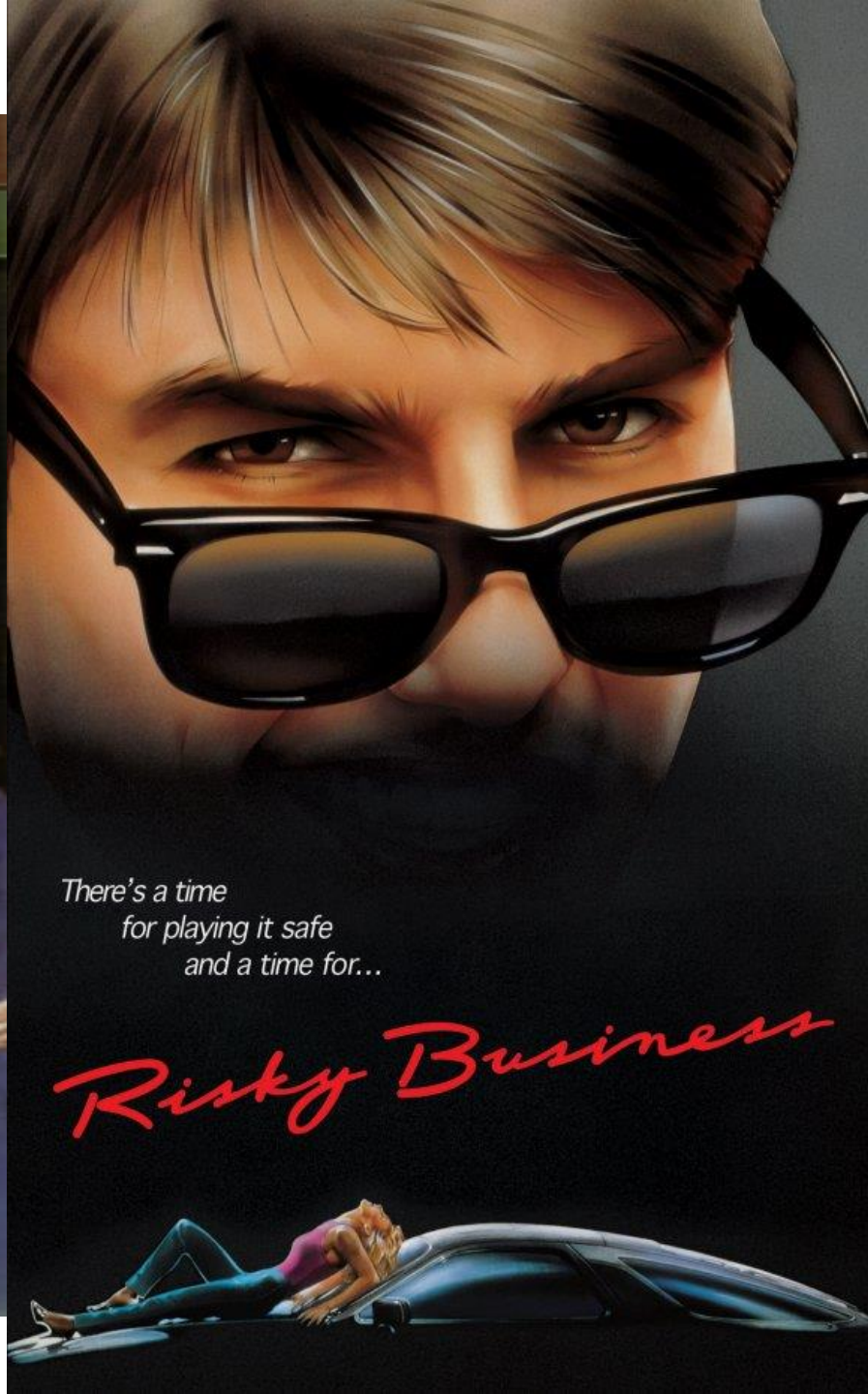
But the number of replacement therapies that would make billion-dollar sellers dwindled by the mid-nineties, and in their stead came mAbs, their fragments and other

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


the Color of Money
THE ORIGINAL MOTION PICTURE SOUNDTRACK
FEATURING
DON HENLEY
ROBERT PALMER
ERIC CLAPTON
MARK KNOPFLER
WILLIE DIXON
B.B. KING
WARREN ZEVON


There's a time
for playing it safe
and a time for...
Risky Business

European Medicines Agency

London 10 November 2008
EMEA/557896/2008

PUBLIC STATEMENT ON

Exubera
(Insulin human)

WITHDRAWAL OF THE MARKETING AUTHORISATION IN THE EUROPEAN UNION

On 24 January 2006 the European Commission issued a marketing authorisation valid throughout the European Union for the medicinal product Exubera, human insulin, 1 mg and 3 mg inhalation powder for inhalation use, which had been approved for the treatment of type II diabetes mellitus[1].

The marketing authorisation holder (MAH) responsible for Exubera was Pfizer Limited. The European Commission was notified by letter dated 26 June 2008 of the MAH's decision to voluntarily withdraw the marketing authorisation for Exubera for commercial reasons.

On 26 September 2008 the European Commission issued a decision to withdraw the marketing authorisation for Exubera. Pursuant to this decision the European Public Assessment Report for Exubera will be updated to reflect that the marketing authorisation is no longer valid.

Novartis Europharm Ltd withdraws its marketing authorisation application for Joulferon (albinterferon alfa-2b)

Novartis Europharm Ltd withdraws its marketing authorisation application for Joulferon (albinterferon alfa-2b)

The European Medicines Agency has been formally notified by Novartis Europharm Ltd of its decision to withdraw its application for a centralised marketing authorisation for the medicine Joulferon (albinterferon alfa-2b), 900 mg powder and solvent for solution for injection in pre-filled pen and vials.

This medicine was intended to be used in combination with ribavirin for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alfa.
The application for the marketing authorisation for Joulferon was submitted to the Agency on 3 December 2009. At the time of the withdrawal it was under review by the Agency's Committee for Medicinal Products for Human Use (CHMP).

In its official letter, the company stated that its decision to withdraw the application was based on preliminary comments of the rapporteurs in the day 80 draft assessment reports that additional new data would be requested for a favourable opinion but that those could not be generated within the timeframe allowed in the centralised procedure.

News & Events

FDA NEWS RELEASE

For Immediate Release: Dec. 16, 2010
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA begins process to remove breast cancer indication from Avastin label

Drug not shown to be safe and effective in breast cancer patients

The U.S. Food and Drug Administration announced today that the agency is recommending removing the breast cancer indication from the label for Avastin (bevacizumab) because the drug has not been shown to be safe and effective for that use.

The agency is making this recommendation after reviewing the results of four clinical studies of Avastin in women with breast cancer and determining that the data indicate that the drug does not prolong overall survival in breast cancer patients or provide a sufficient benefit in slowing disease progression to outweigh the significant risk to patients. These risks include severe high blood pressure; bleeding and hemorrhage; the development of perforations (or "holes") in the body, including in the nose, stomach, and intestines; and heart attack or heart failure.

In July 2010, after reviewing all available data an independent advisory committee, composed primarily of oncologists, voted 12-1 to remove the breast cancer indication from Avastin's label.

"After careful review of the clinical data, we are recommending that the breast cancer indication for Avastin be removed based on evidence from four independent studies," Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research. "Subsequent studies failed to confirm the benefit observed in the original trial. None of the studies demonstrated that patients receiving Avastin lived longer and patients receiving Avastin experienced a significant increase in serious side effects. The limited effects of Avastin combined with the significant risks led us to this difficult decision. The results of these studies are disappointing. We encourage the company to conduct additional research to identify if there may be select groups of patients who might benefit from this drug."

Removing the breast cancer indication from the Avastin label will be a process. This is the first step. The drug itself is not being removed from the market and today's action will not have any immediate impact on its use in treating breast cancer. Today's action will not affect the approvals for colon, kidney, brain, and lung cancers.

Oncologists currently treating patients with Avastin for metastatic breast cancer should use their medical judgment when deciding whether a patient should continue treatment with the drug or consider other therapeutic options.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

03 May 2011
EMA/CHMP/306549/2011 – Corr[1]
Patient Health Protection

Monthly Report

Committee for Medicinal Products for Human Use (CHMP)

11 – 14 April 2011

Re-examination procedure on Avastin concluded

Following re-examination of its previous negative opinion, the Committee adopted a final positive opinion by majority, recommending that the therapeutic indications of **Avastin** (bevacizumab), from Roche Registration Ltd, should be extended to include first-line treatment in combination with capecitabine of patients with metastatic breast cancer in whom treatment with other chemotherapy options, including taxanes or anthracyclines, is not considered appropriate.

A question-and-answer document with more information about this re-examination procedure is available on the Agency's website.

European Medicines Agency

London, 17 April 2009
EMEA/83006/2009

SCIENTIFIC CONCLUSIONS

RAPTIVA

International Nonproprietary Name:
efalizumab

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE SUSPENSION OF RAPTIVA PRESENTED BY THE EMEA

Efalizumab (RAPTIVA) is a recombinant humanized monoclonal antibody that binds specifically to the CD11 a subunit of lymphocyte function-associated antigen-1 (LFA-1), a leukocyte cell surface protein.

Raptiva was authorised in the EU on 20 September 2004. It is indicated for the *"treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA."*

Recently four (three confirmed and one suspected) cases of, progressive multifocal leukoencephalopathy (PML) in psoriatic patients under long-term treatment with efalizumab have been identified prompting a re-evaluation of the benefit-risk. Two confirmed cases were fatal and the one suspected case as well.

Efalizumab was the first biological approved for the treatment of moderate to severe psoriasis in 2004 in so-called "high-need" patients, i.e. those who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies. The indication was granted in this last line therapy on the grounds of a limited efficacy and lack of long term safety data.

Benefit/Risk Balance

The efficacy of Raptiva in psoriasis is modest.

The new safety signals that have emerged (especially PML) together with the known risk of opportunistic infections do compromise the benefit/risk ratio. Since the grant of the Marketing Authorisation, the safety issues have arisen leading to the addition of a number of warnings into the SPC such as aseptic meningitis, immune mediated haemolytic anaemia, antibody development with vaccinations, interstitial pneumonitis, arthritis, erythema multiforme, inflammatory polyradiculoneuropathy Miller Fisher syndrome, facial palsy and Bells palsy and severe infections, malignancies during long-term use, including serious (fatal) events such as opportunistic infections and Guillain Barré syndrome (GBS). In addition the MAH recently notified the EMEA about 3 cases of encephalopathy and 5 cases of encephalitis.

Furthermore, based on a comparative evaluation of serious adverse events, it appears that Raptiva has an unfavourable safety profile as compared to the other biologicals with respect to fatal reports, fatal infections neoplasm and neurological disorder.

It is questioned by the CHMP whether a psoriasis population can be identified that exclusively benefits from efalizumab. As indicated by the experts there might be a small group of patients who could benefit from Raptiva. However the CHMP considered that no further risk minimisation measures would be effective for this group. Moreover it might be that this group of patients naturally would be at higher risk.

Therefore on the basis of the above, the CHMP concluded that the benefit/risk of Raptiva is considered negative.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 May 2010
EMA/430923/2010
Patient Health Protection

Assessment report for TYSABRI

International Non-proprietary Name: natalizumab

Procedure No. EMA/H/C/000603/A20/0029

1. Executive summary

Tysabri (Natalizumab) was granted a Marketing Authorisation on 27 June 2006 for use as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) in patients with high disease activity despite treatment with a beta-interferon or in patients with rapidly evolving severe relapsing remitting multiple sclerosis.

With increasing post-marketing experience and duration of exposure to natalizumab, the continued reporting of MS patients diagnosed with PML has raised concerns, especially because these data suggest, that risk for developing PML increases significantly after two years of continuous exposure.

On 22 October 2009, the CHMP requested a Review of the benefits and risks for Tysabri in view of new cases of progressive multifocal leukoencephalopathy (PML) that have been observed since Tysabri has been on the market and in consideration of the occurrence of IRIS in these patients once Tysabri has been stopped and PLEX and/or immunoabsorption has been implemented.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 26 October 2009 to assess the above concerns and its impact on the benefit/risk for Tysabri, and to give its opinion on measures necessary to ensure the safe use of Tysabri, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

3. Discussion and Benefit/risk assessment

The CHMP concluded that the benefit still outweighs the risks for the patients treated with Tysabri. The CHMP also concluded that the Product Information for Tysabri should include safety information aiming at informing patients and physicians about the risk of PML so that the symptoms are detected as soon as possible and therefore recommended the amendments to the relevant sections of the Summaries of Product Characteristics and Package Leaflet

In addition the Conditions of the Marketing Authorisation (Annex II) as well as the Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States (Annex IV) were also amended.

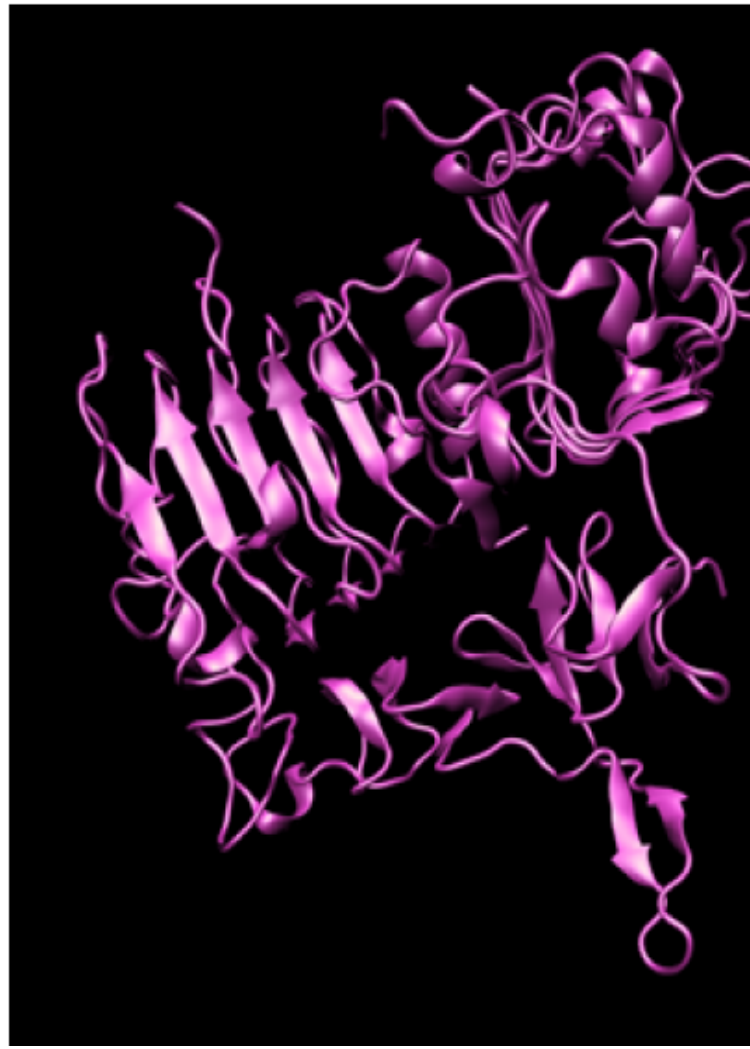
The CHMP also recommended that a dialogue is put continuously in place between the MAH and the Regulatory Authorities for further updates on the implementation of the risk minimisation measures as well on the scientific developments currently ongoing to further investigate PML.

Benefit/Risk Balance

Taken this into account, the benefit/risk balance for natalizumab is considered favourable.

Biological therapies: how can we afford them?

Demand for biological drugs is putting pressure on health budgets. **Christopher Kelly** and **Fraz Mir** examine why they are so expensive and what can be done to increase access



The success of biopharmaceuticals is producing a growing problem for public healthcare services worldwide. Newer biological therapies offer fresh hope for the treatment sures of cuts in public spending, to survive in the current financial climate. We examine the reasons for the high costs and the possibilities for reducing them.

COMMISSION DIRECTIVE 2003/63/EC

of 25 June 2003

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

Biosimilars in the EU

general considerations

- Marketing authorization through the centralized procedure (biotechnological products)
- Same pharmaceutical form, dose and route of administration as the reference product
- No extrapolation between different routes of administration
- The reference product should be the same throughout the dossier and it should be available in the EU

Biosimilars in the EU

general considerations

- Preclinical Comparative studies *in vitro* and *in vivo*
  - PK
  - PD
  - Immunogenicity
  - Toxicity

- Efficacy and safety data showing comparability
- Immunogenicity data
- **Pharmacovigilance system and risk management plan**

COMMISSION DIRECTIVE 2003/63/EC

of 25 June 2003

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

— Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.

— Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.

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

Human medicines
- Pre-authorisation
- Post-opinion
- Post-authorisation
- Product information
- Scientific advice and protocol assistance
- Scientific guidelines
  - Search guidelines
  - Quality
  - Q&A on quality
  - Biologicals
  - Non-clinical
  - Clinical efficacy and safety
  - Multidisciplinary
    - Paediatrics
    - Cell therapy and tissue engineering
    - Vaccines
    - Biosimilar
    - Gene Therapy
    - Herbal medicinal products
    - Pharmacogenomics

Home ▸ Regulatory ▸ Human medicines ▸ Scientific guidelines ▸ Multidisciplinary ▸ Biosimilar

Multidisciplinary: Biosimilar

This page lists the European Medicines Agency's scientific guidance documents on biosimilar medicines.

If you have comments on a document that is open for consultation, use the form for submission of comments on scientific guidelines.

Table of contents

Overarching biosimilar guidelines

Back to top

Topic	Documents	Reference number	Publication date	Effective date	Remarks
Revision of the guideline on similar biological medicinal product	Concept paper	CHMP/BMWP/572643/2011	Released for consultation November 2011		Deadline for comments 29 February 2012
Revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues	Concept paper	EMA/CHMP/BMWP/572828/2011	Released for consultation October 2011		Deadline for comments 31 December 2011
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	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 May 2013
CHMP/437/04 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Similar Biological Medicinal Products

Draft

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

This guideline replaces the Guideline on similar biological medicinal products (CHMP/437/04).

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 difference would have to be duly justified with regard to their potential impact on safety and efficacy and could contradict the biosimilar principle. Differences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) should be explained, but may not preclude biosimilarity. If the biosimilar comparability exercise indicates early on that there are significant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will eventually be established, a stand-alone development should be considered instead.

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 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, population, endpoints and conduct to detect such differences.

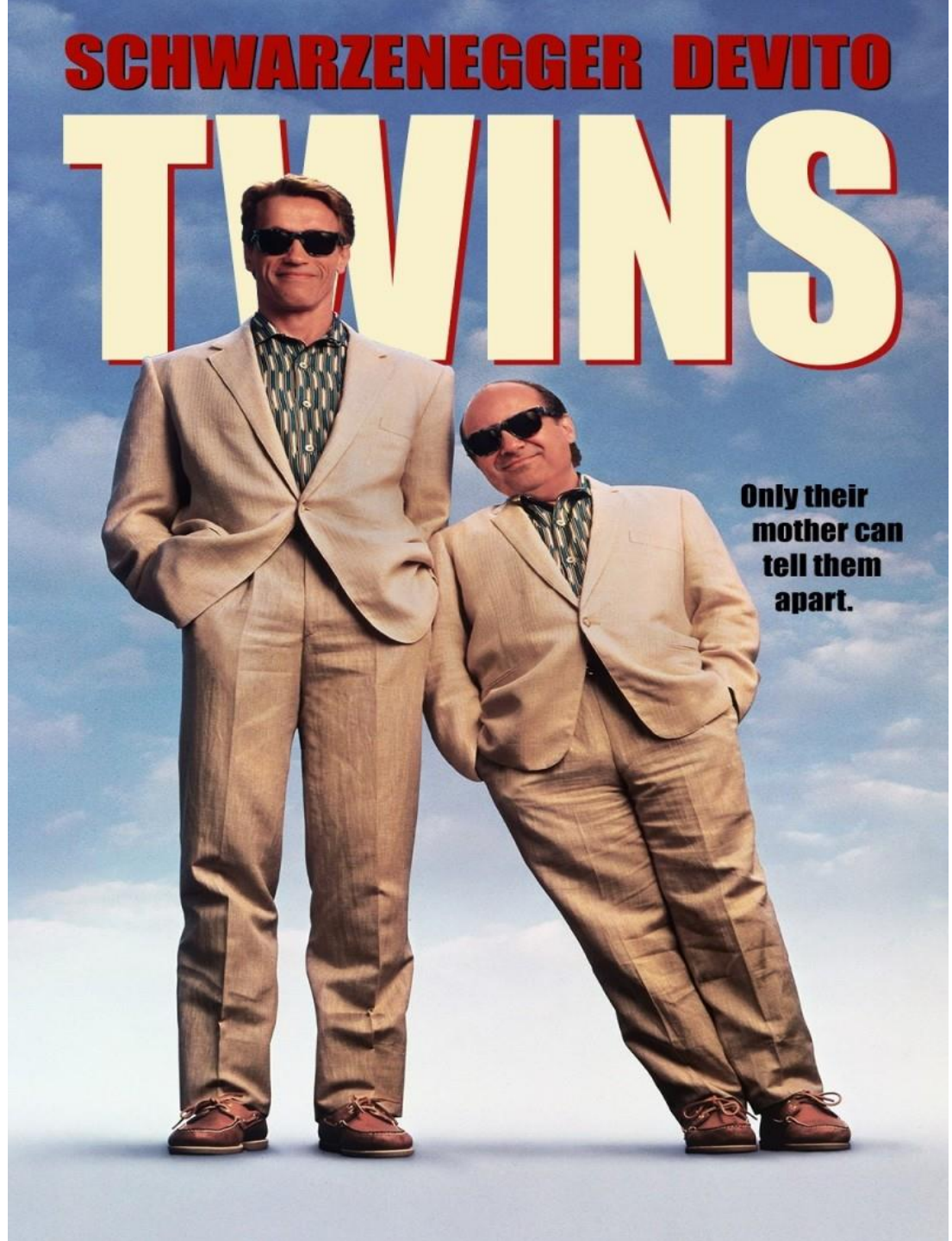
5.3.1. Study designs

In general, an equivalence design should be used. The use of a non-inferiority design may be acceptable if justified on the basis of a strong scientific rationale and taking into consideration the characteristics of the reference product, e.g. safety profile/tolerability, dose range, dose-response relationship. A non-inferiority trial may only be accepted where the possibility of increased efficacy can be excluded on scientific and mechanistic grounds. However, as in equivalence trials assay sensitivity has to be considered.

It is recommended to discuss the use of a non-inferiority design with regulatory authorities.

5.3.2. Efficacy endpoints

Efficacy trials of biosimilar medicinal products do not aim at demonstrating efficacy per se, since this has already been established with the reference product. The sole purpose of the efficacy trials is to investigate whether a clinically significant difference between the reference and biosimilar products can be detected.


SCHWARZENEGGER DEVITO
TWINS
Only their mother can tell them apart.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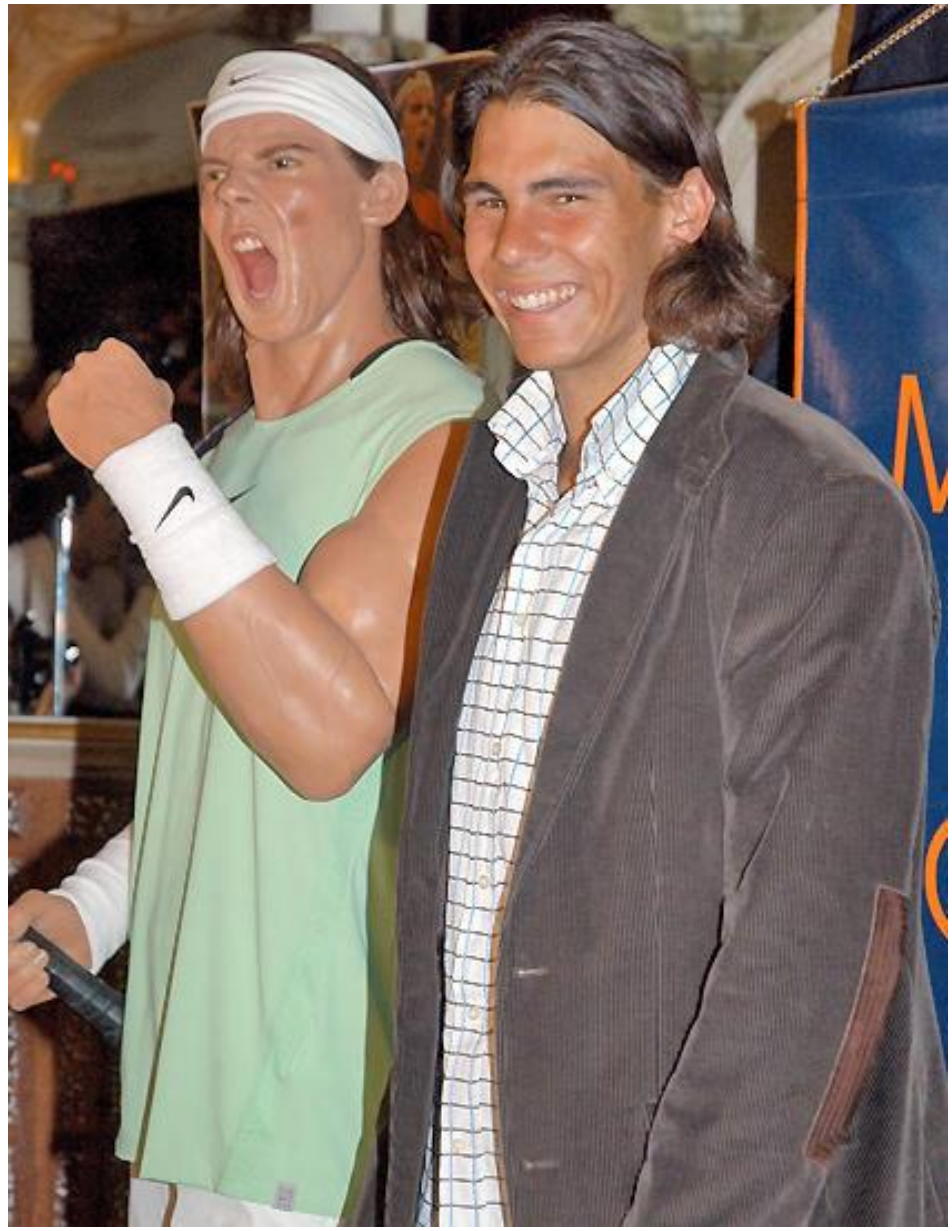


ALMOST IDENTICAL

biosimilars

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30/07/2014

Medicine Name	Active Substance	Marketing Authorisation Holder	Status	Authorisation date
Abasria	**rhu insulin**		**Authorised**	
Abseamed	epoetin alfa	Medice Arzneimittel Pütter GmbH	Authorised	28/08/2007
Accofil	**filgrastim**		**Authorised**	
Alpheon	rhu IFNalfa-2a	BioPartners GmbH	Refused	-
Bemfola	follitropin alfa	Finox Biotech AG	Authorised	27/03/2014
Binocrit	epoetin alfa	Sandoz GmbH	Authorised	28/08/2007
Biograstim	filgrastim	AbZ-Pharma GmbH	Authorised	15/09/2008
Epoetin Alfa Hexal	epoetin alfa	Hexal AG	Authorised	28/08/2007
Filgrastim Hexal	filgrastim	Hexal AG	Authorised	06/02/2009
Filgrastim ratiopharm	filgrastim	Ratiopharm GmbH	Withdrawn	15/09/2008
Grastofil	filgrastim	Apotex Europe BV	Authorised	18/10/2013
Inflectra	infliximab	Hospira UK Limited	Authorised	10/09/2013
Nivestim	filgrastim	Hospira UK Ltd.	Authorised	08/06/2010
Omnitrope	somatropin	Sandoz GmbH	Authorised	12/04/2006
Ovaleap	follitropin alfa	Teva Pharma B.V.	Authorised	27/09/2013
Ratiograstim	filgrastim	Ratiopharm GmbH	Authorised	15/09/2008
Remsima	infliximab	Celltrion Healthcare Hungary Kft.	Authorised	10/09/2013
Retacrit	epoetin zeta	Hospira UK Limited	Authorised	18/12/2007
Silapo	epoetin zeta	Stada Arzneimittel AG	Authorised	18/12/2007
Tevagrastim	filgrastim	Teva GmbH	Authorised	15/09/2008
Valtropin	somatropin	BioPartners GmbH	Withdrawn	24/04/2006
Zarzio	filgrastim	Sandoz GmbH	Authorised	06/02/2009

Terapias avanzadas

when the rubber hits the road...

07/2007	**CEREPRO**	AdV-HSVtk. Withdrawn by the applicant before the final negative opinion on the 2nd application
12/2008	**ADVEXIN**	AdV-p53. Withdrawn by the applicant before the final negative opinion
07/2009	**CHONDROCELECT**	Autologous chondrocytes. Marketing authorization granted
07/2012	**GLYBERA**	AAV-LPL. Marketing authorization granted after 4rd evaluation
01/2013	**HYALOGRAFT C AUTOGRAFT**	Autologous chondrocytes. Withdrawn by the applicant before the negative opinion
03/2013	**ORANERA**	Autologous oral mucosal epithelial cells. Withdrawn by the applicant before the negative opinion
04/2013	**MACI**	Matrix-induced autologous chondrocyte implantation. Marketing authorization granted
06/2013	**PROVENGE**	Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T). Marketing authorization granted

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