IV Simposio

GETHI

Brekthrough designations & Acceso off-label

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Organizado por: Grupo Gethi – Grupo Español de Tumores Huérfanos e Infrecuentes

CENTRO INTEGRAL ONCOLÓGICO hm CIOCC

Disclaimers

- The views presented are personal and may not be understood or quoted as being made on behalf of or reflecting the position of AEMPS, EMA or one of its committees or working parties

- Data presented have been sourced from European Public Assessment Reports (EPARs) and published literature

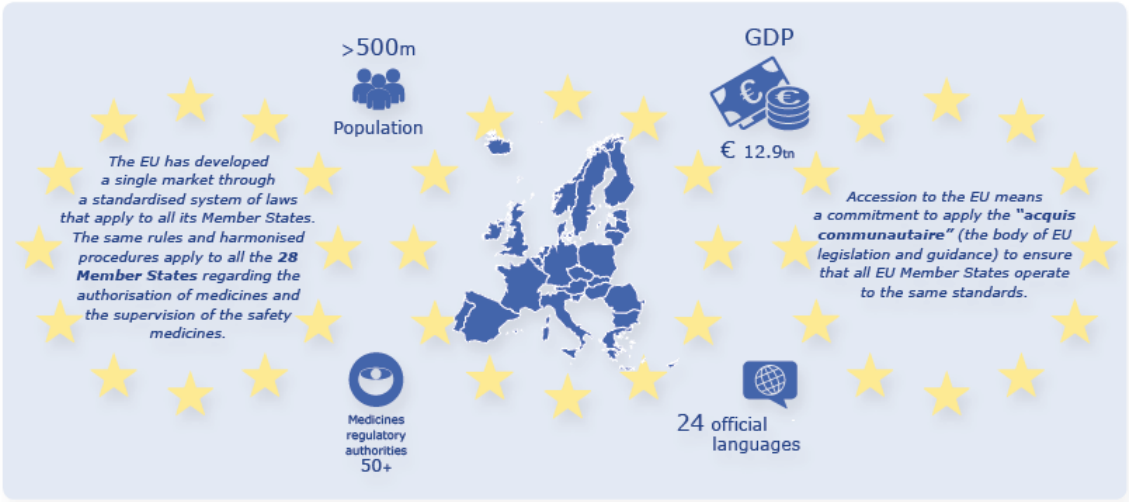
MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

agencia española de medicamentos y productos sanitarios

The European regulatory system for medicines

A consistent approach to medicines regulation across the European Union

The European Union – key facts



EU Member States: 28

The European Economic Area (EEA) is formed of the 28 EU Member States plus:

The EU regulatory system for medicines

The European medicines regulatory system is based on a network of around 50 regulatory authorities from the 31 EEA countries (28 EU Member States plus Iceland, Liechtenstein and Norway), the European Commission and EMA. This network is what makes the EU regulatory system unique.

Pricing and reimbursement

Once a marketing authorisation has been granted, decisions about price and reimbursement take place at the level of each Member State considering the potential role and use of the medicine in the context of the national health system of that country.

Marketing authorisations

To protect public health and ensure the availability of high quality, safe and effective medicines for European citizens, all medicines must be authorised before they can be placed on the market in the EU. The European system offers different routes for such an **authorisation**.

Structure: **decentralised body** responsible for coordination of scientific/regulatory expertise in national competent authorities (NCAs) from EU member states and external experts network

The **centralised procedure** allows the marketing of a medicine on the basis of a single EU-wide assessment and marketing authorisation which is valid throughout the EU. Pharmaceutical companies submit a single authorisation application to EMA.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Which products must be centrally authorised?

- All human medicines derived from **biotechnology** and other high-tech processes

- New active substances intended for:

  - **HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune** and other immune dysfunctions, and **viral diseases**

- **Orphan** medicines

The Agency's Committee for Medicinal Products for Human Use (CHMP) or Committee for Medicinal Products for Veterinary Use (CVMP) then carries out a scientific assessment of the application and gives a recommendation to the European Commission on whether or not to grant a marketing authorisation. Once granted by the European Commission, the centralised marketing authorisation is valid in all EU Member States. The use of the centrally authorised procedure is compulsory for most innovative medicines, including medicines for rare diseases.

EMA enables one application, one assessment, one market authorisation for the whole of the EU.

The Committee for Medicinal Products for Human Use (CHMP) establishes a number of working parties at the beginning of each three-year mandate. These working parties have expertise in a particular scientific field, and are composed of members selected from the list of European experts maintained by the Agency.

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 drafting groups are:

- Excipients Drafting Group
- Gastroenterology Drafting Group
- Radiopharmaceuticals Drafting Group
- Respiratory Drafting Group

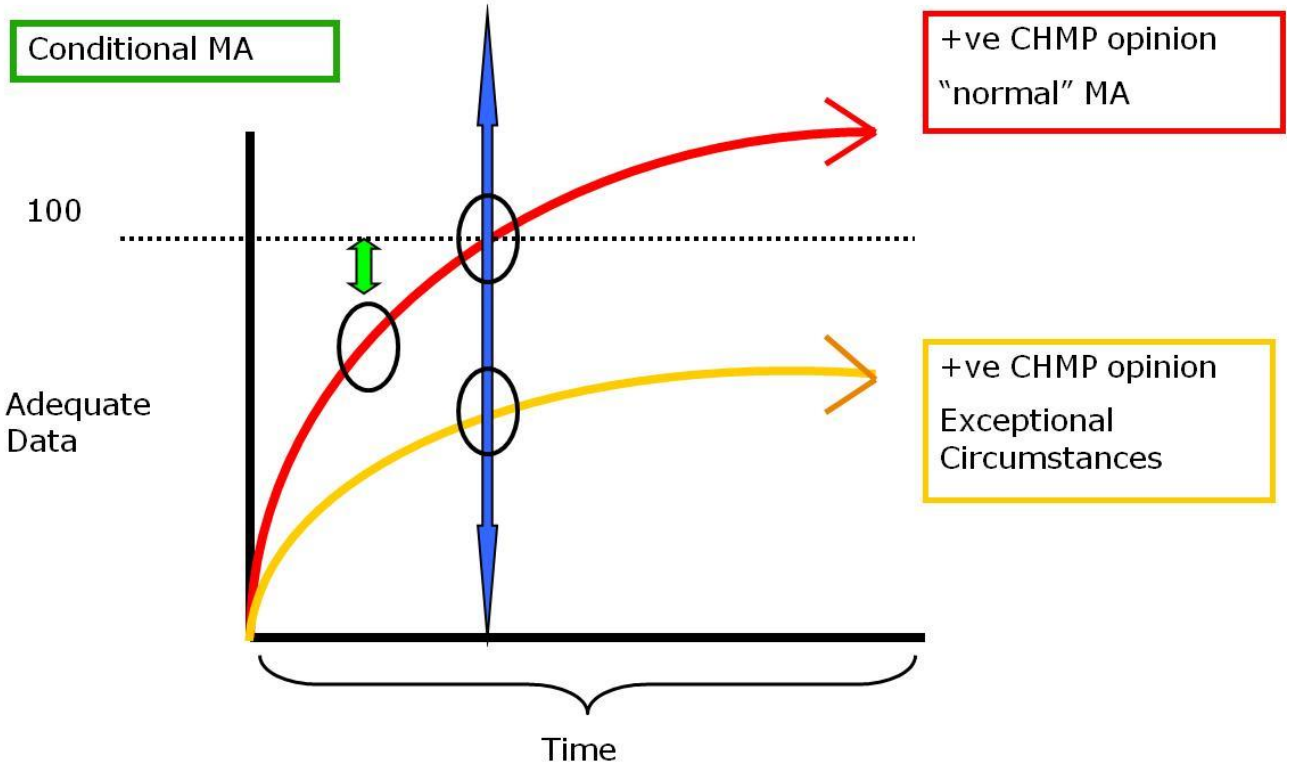
The current CHMP scientific advisory groups are:

- Scientific Advisory Group on Cardiovascular Issues
- Scientific Advisory Group on Anti-infectives
- Scientific Advisory Group on Diabetes/Endocrinology
- Scientific Advisory Group on HIV / Viral Diseases
- Scientific Advisory Group on Neurology
- Inter-Committee Scientific Advisory Group on Oncology
- Scientific Advisory Group on Psychiatry
- Scientific Advisory Group on Vaccines

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

Type of authorisation



Conditional Marketing Authorisation (CMA)

Early approval mechanism (less complete clinical evidence at time of approval)

- Requirements: Serious/orphan conditions, provided that
  - The benefit-risk balance of the product is positive
  - It is likely that the applicant will be able to provide comprehensive data
  - Immediate availability outweigh the risks related to uncertainties of the missing data
  - **CHMP to judge if unmet medical needs will be fulfilled**
    - **there exists no satisfactory method** authorised in the Community, or,
    - even if such a method exists, in relation to which **the medicinal product concerned will be of major therapeutic advantage** to those affected

Regulation (EC) No 507/2006

No satisfactory method

- Has to be justified on a case-by-case basis
  - **No medicinal product approved**
  - Necessary to introduce new methods when existing **methods used in clinical practice** (if any) are **unsatisfactory** (**quantify**)
  - Extent to which **the medicinal product will address** the unmet medical need (**quantify**)

Guideline on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004

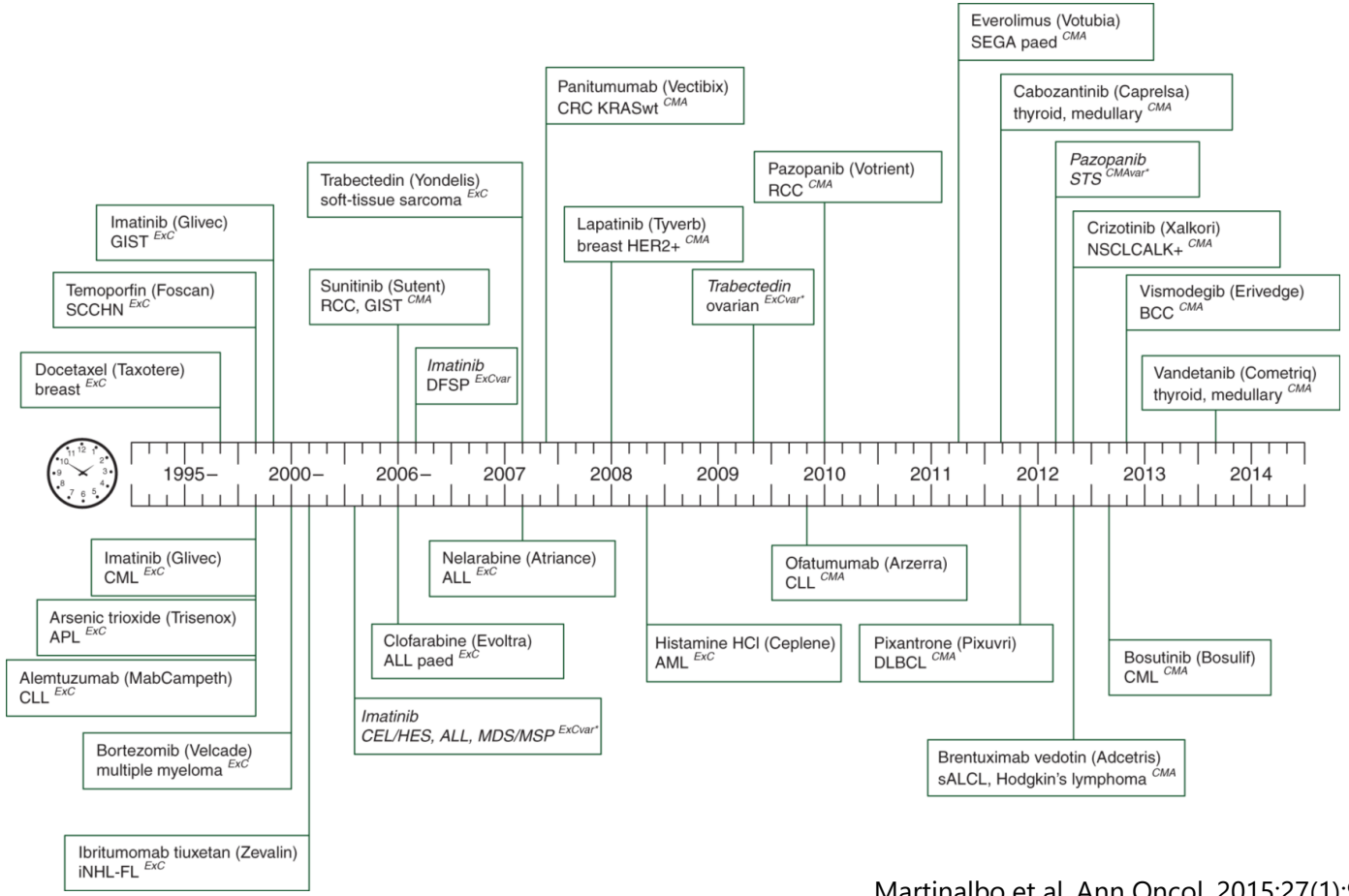
Major Therapeutic Advantage (MTA)

- Advantages should be **demonstrated** over existing methods used in clinical practice (if any)
- Has to be justified on a case-by-case basis
  - Normally, **meaningful improvement of efficacy** or clinical safety
  - Major improvements to **patient care** (e.g., compliance, ease of administration)
  - **Quantify** the unmet medical need based on medical or epidemiologic data

Guideline on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004

Approval based on Non-RCT trials

- Large magnitude, durable ORR ("**dramatic activity**")
- Mechanism of action supported by strong scientific rationale or preclinical data
- Well-defined patient population
- Substantial, durable tumour responses that clearly exceed those offered by any existing available therapies
- The benefits outweigh the risks



Martinalbo et al. Ann Oncol. 2015;27(1):96-1

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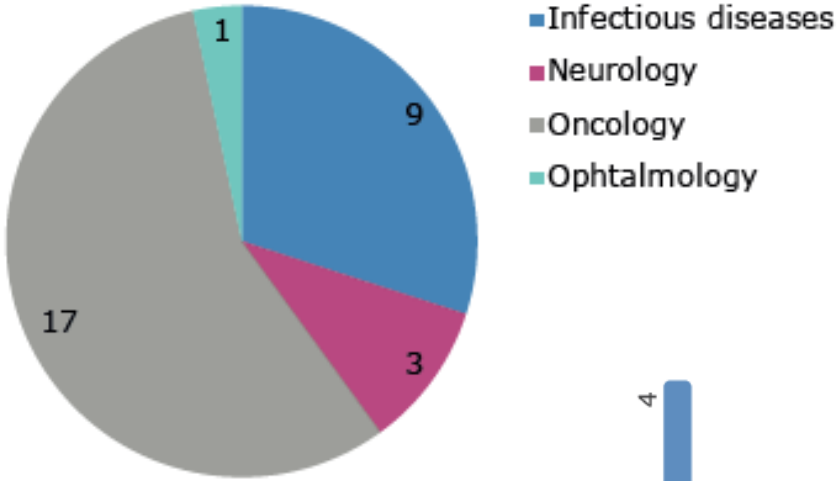
agencia española de medicamentos y productos sanitarios

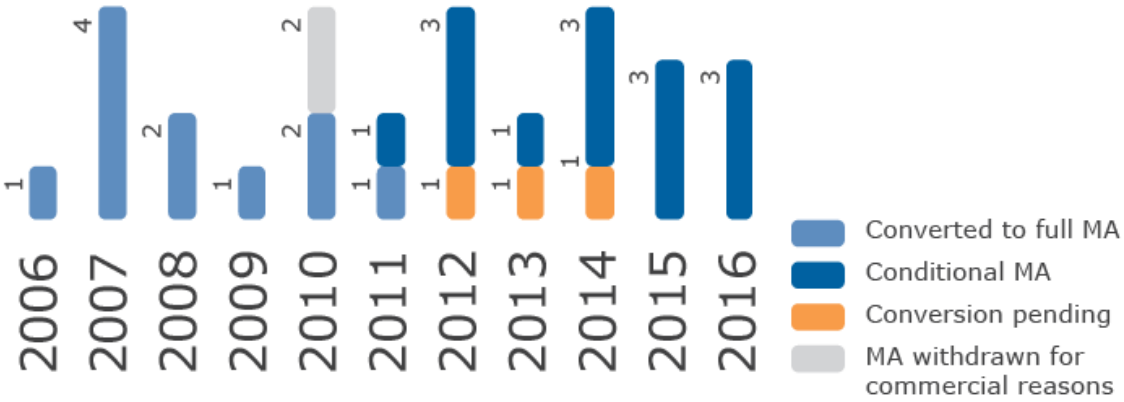
30 CMAs

- 24 Target debilitating or life-threatening conditions
- 14 Are orphan medicines
- 3 Address emergency situations linked to a public health threat

By therapeutic area

- 17 Oncology
- 9 Infectious diseases
- 3 Neurology
- 1 Ophthalmology





Conditional marketing authorisations

Three medicines received a recommendation for a conditional marketing authorisation, one of the possibilities in the EU to give patients early access to new medicines. This tool allows for the early approval of a medicine on the basis of less complete clinical data than normally required if the medicine addresses an urgent unmet medical need. These medicines are subject to specific post-authorisation obligations for medicine developers to obtain complete data on the medicine.

Endocrinology

Natpar

treatment for patients with chronic hypoparathyroidism who cannot be adequately controlled with standard treatment with calcium and vitamin D.

Post-authorisation obligations:

The company will conduct a further study to confirm the benefits an d risks of the medicine and the appropriateness of the once-a-day dosing schedule.

Crysvita

treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children and adolescents with growing skeletons.

Post-authorisation obligations:

The company will:

- Provide updated results from two ongoing studies in children aged between 5 and 12 years and between 1 and 4 years.
- Conduct and submit the results of a study comparing Crysvita with oral phosphate and active vitamin D in children with X-linked hypophosphataemia.

Cancer

Bavencio

treatment of metastatic Merkel cell carcinoma.

Post-authorisation obligations:

The company will provide further data from the ongoing study of patients who did not receive chemotherapy before starting treatment with Bavencio.

Accelerated assessment

Accelerated assessment reduces the timeframe for the European Medicine Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) to review a marketing-authorisation application. Applications may be eligible for accelerated assessment if the CHMP agrees the product is of major interest for public health and in particular from the viewpoint of therapeutic innovation.

Evaluating a marketing-authorisation application under the centralised procedure can take up to 210 days, not counting clock stops when applicants have to provide additional information. On request, the CHMP can reduce the timeframe to 150 days if the applicant provides sufficient justification for an accelerated assessment.

Accelerated assessments

Seven medicines received a recommendation for marketing authorisation following an accelerated assessment. This mechanism is reserved for medicines that are able to address unmet medical needs. It allows for faster assessment of eligible medicines by EMA's scientific committees (within up to 150 days rather than up to 210 days).

Neurology

Brineura

to treat neuronal ceroid lipofuscinosis type 2 (CLN2) disease.

Oxervate

for the treatment of moderate to severe neurotrophic keratitis.

Spinraza

to treat patients with spinal muscular atrophy.

Verkazia

to treat severe vernal keratoconjunctivitis in children and adolescents.

Infections

Maviret

for the treatment of chronic hepatitis C virus (HCV) infection.

Vosevi

for the treatment of chronic hepatitis C virus (HCV) infection.

Gastroenterology

Jorveza

to treat eosinophilic esophagitis, a rare inflammatory condition of the oesophagus.

Approval under exceptional circumstances

Two medicines were authorised under exceptional circumstances, a route that allows patients access to medicines that cannot be approved under a standard authorisation as comprehensive data cannot be obtained, either because there are only very few patients with the disease, or the collection of complete information on the efficacy and safety of the medicine would be unethical, or there are gaps in the scientific knowledge. These medicines are subject to specific post-authorisation obligations and monitoring.

Cancer

Qarziba

(previously Dinutuximab beta Apeiron) - for the treatment of high-risk neuroblastoma.

Post-authorisation obligations:

The company will:

- Monitor the safety of the medicine using a patient registry and provide yearly updates.
- Perform tests to obtain more information on how the medicine is processed by the body and how the immune system responds to the medicine.
- Provide the results of a study looking at the effect of giving Qarziba together with interleukin-2.
- Report on the 5-year survival rates of patients who took part in studies.

Neurology

Brineura

to treat neuronal ceroid lipofuscinosis type 2 (CLN2) disease.

Post-authorisation obligations:

The company will provide further data from studies on the safety of Brineura, including the risk of allergic reactions when used long-term, and on its long-term effectiveness in delaying or stopping worsening of movement and language skills. The studies will include children below 2 years of age, for whom there are currently no data.

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Scientific advice and protocol assistance

For medicines for human use

The European Medicines Agency offers scientific advice and protocol assistance to facilitate the development and availability of medicines

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agencia española de medicamentos y productos sanitarios

- The goal is to **foster research on and development** of medicines for patients whose diseases cannot be treated or who need better treatment options to help them live healthier lives

- It provides early and enhanced scientific and regulatory support to medicines that have the **potential** to significantly address patients' **unmet medical needs**.

Benefits of PRIME

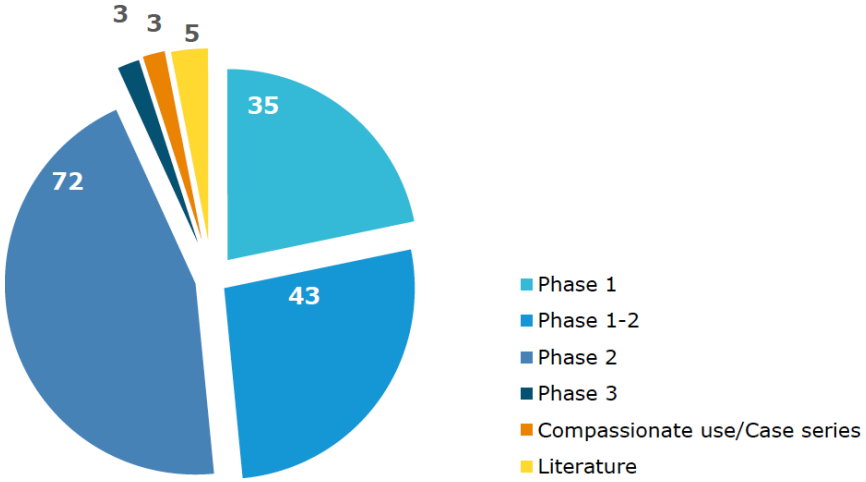
FOR PATIENTS

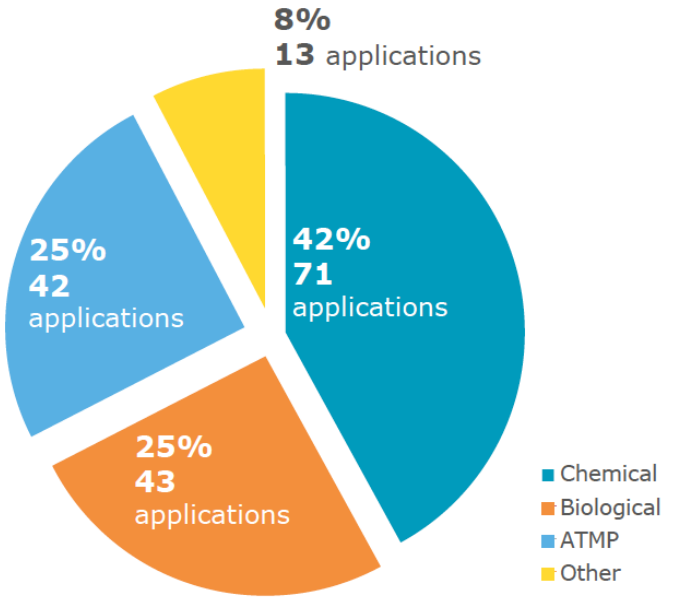
- PRIME is driven by patients' needs.
- It focuses on medicines that **address an unmet medical need**, i.e. offer a major therapeutic advantage over existing treatments, or benefit patients with no current treatment options for their disease.
- It helps to translate research into the development of medicines while meeting regulatory requirements.
- It aims to **bring promising treatments to patients earlier**, without compromising high evaluation standards and patient safety.

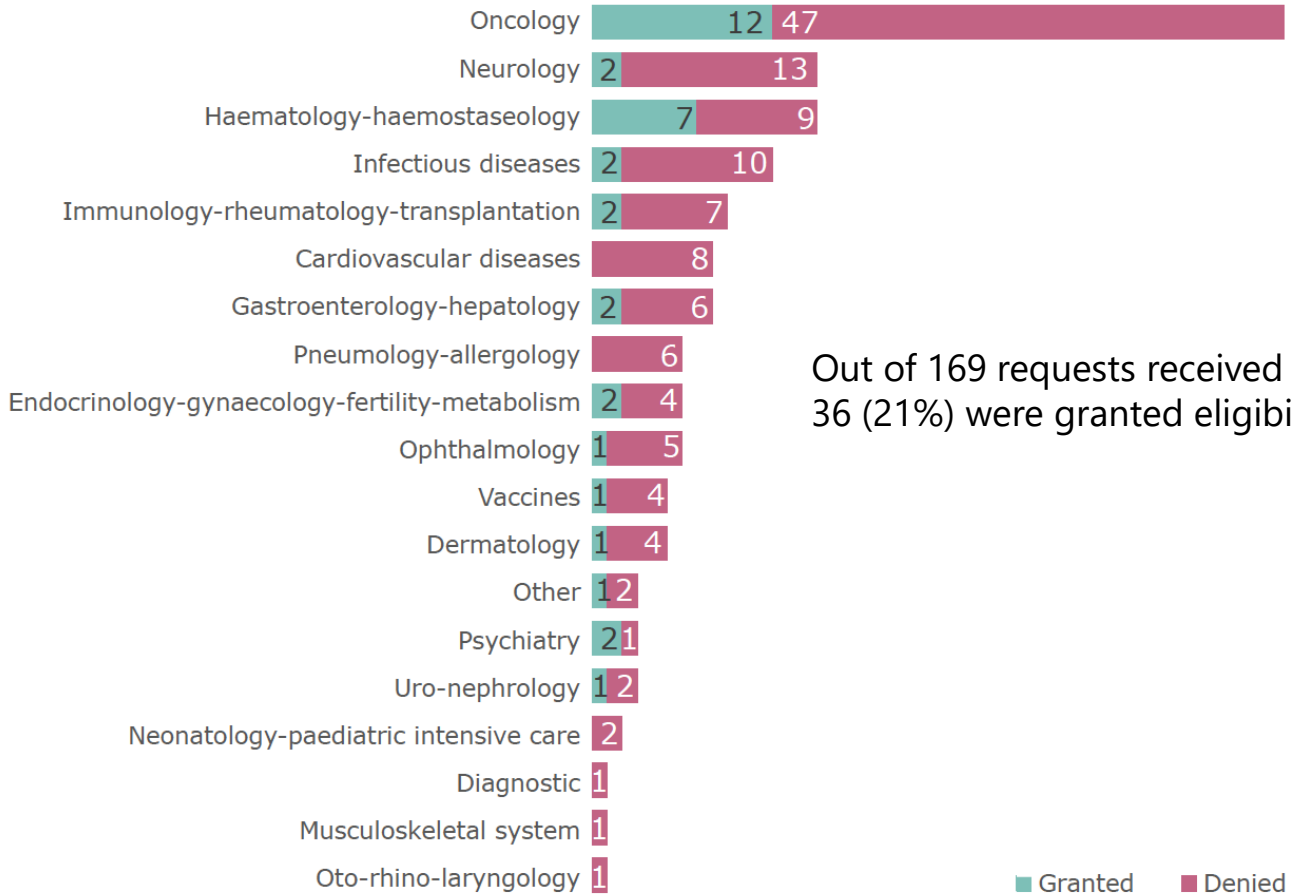
FOR MEDICINE DEVELOPERS

- PRIME helps developers of promising new medicines to optimise development plans.
- It fosters early dialogue with EMA to facilitate robust data collection and high quality marketing authorisation applications.
- It speeds up evaluation so that medicines can reach patients earlier.
- It encourages developers to focus resources on medicines likely to make a real difference to patients' lives.

- PRIME aims to bring promising medicines that meet regulatory requirements to patients earlier by optimising and supporting their development.
- The scheme focuses on medicines that address an unmet medical need and that have the potential to bring a major therapeutic advantage to patients.
- With PRIME, EMA translates scientific advances into the development of medicines that can make a real difference to patients' lives.







Out of 169 requests received and assessed, 36 (21%) were granted eligibility to PRIME

PRIME: in brief

Medicines eligible for PRIME must address an unmet medical need.

Preliminary data must be available showing the potential to address this need and bring a major therapeutic advantage to patients.

EMA will provide early and enhanced support to optimise the development of eligible medicines, speed up their evaluation and contribute to timely patients' access.

Special support for SMEs and academia

Micro-, small- and medium-sized enterprises (SMEs) and applicants from the academic sector can apply for PRIME at an earlier stage of development when they have compelling non-clinical data and tolerability data from initial clinical trials. They may also request a fee waiver for scientific advice.

SMEs and academia can particularly benefit from earlier scientific and regulatory support since they often lack experience with the regulatory framework.

• In the context of all this learning, which has ultimately led to several new (breakthrough) drugs a number of uncertainties are also increasingly being identified

• There are **uncertainties** related to knowledge and others linked to **access**

Parallel EMA/HTA scientific advice

Applicants can seek CHMP scientific advice/ protocol assistance in parallel with advice from health-technology-assessment (HTA) bodies.

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European Commission

STRENGTHENING COOPERATION ON HEALTH TECHNOLOGY ASSESSMENT

NEW MEDICINES

EU ASSESSMENT
(jointly done by the Member States)

NATIONAL ASSESSMENT

CLINICAL ASSESSMENT
(benefits compared to existing treatments)

NON-CLINICAL ASSESSMENT
(economic, social and ethical aspects)

NEW MEDICAL DEVICES

High-risk devices with high impact on patients, public health and EU health systems

CLINICAL ASSESSMENT
(benefits compared to existing treatments)

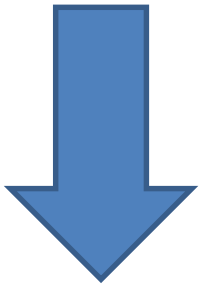
NON-CLINICAL ASSESSMENT
(economic, social and ethical aspects)

Compassionate use

Compassionate use is a treatment option that allows the use of an unauthorised medicine. Under strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorised therapies and who cannot enter clinical trials.

The European Medicines Agency (EMA) provides recommendations through the Committee for Medicinal Products for Human Use (CHMP), but these do not create a legal framework. Compassionate use programmes are coordinated and implemented by Member States, which set their own rules and procedures.

EL USO COMPASIVO NO DEBE SUSTITUIR A LOS ENSAYOS CLÍNICOS NI ENTORPECER EL DESARROLLO DE LOS MISMOS



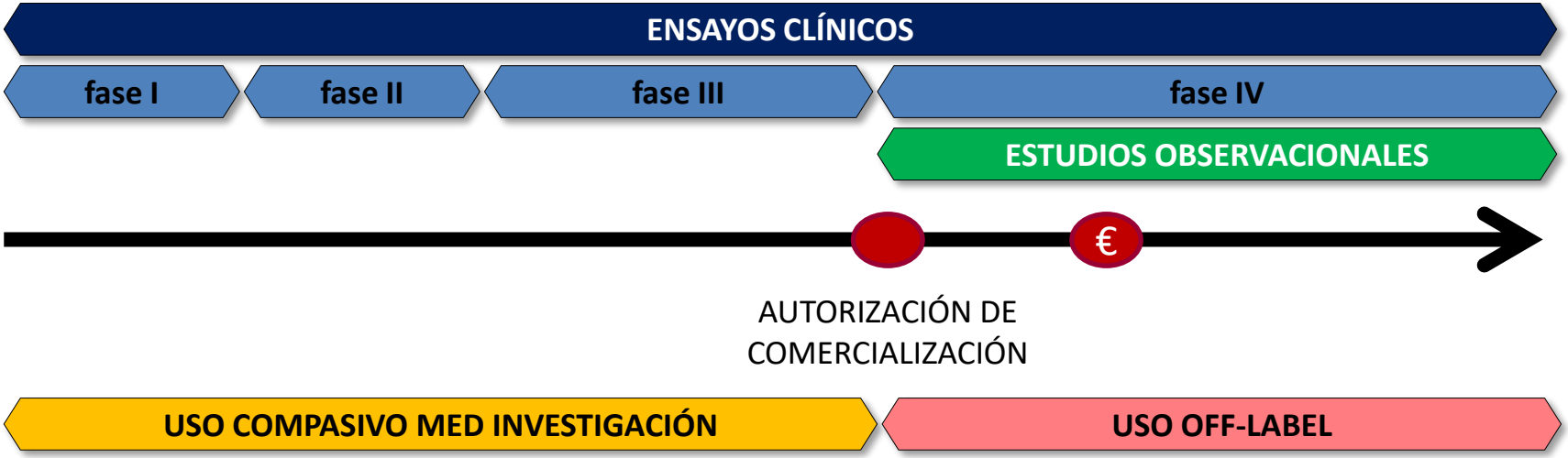
BENEFICIO PARA EL PACIENTE

USO COMPASIVO

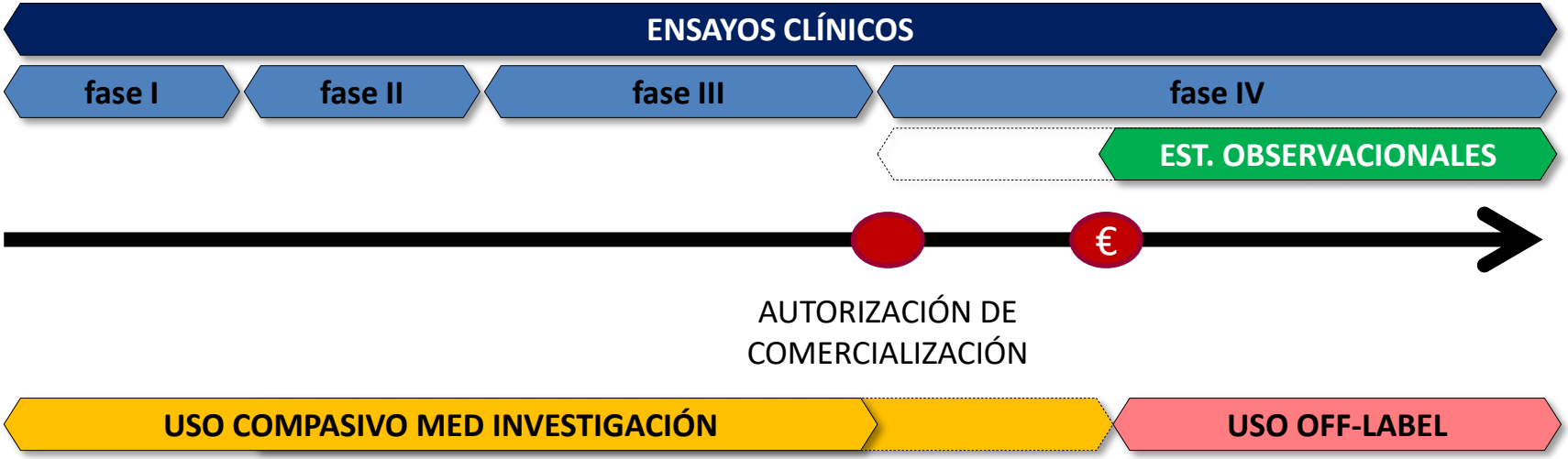
- Uso de un medicamento en pacientes que padecen una enfermedad crónica o gravemente debilitante o que se considera pone en peligro su vida (retraso en acceso es pérdida de oportunidad) y que no pueden ser tratados satisfactoriamente con un medicamento autorizado (necesidad médica no cubierta).

- El medicamento de que se trate deberá estar sujeto a una solicitud de autorización de comercialización, o bien deberá estar siendo sometido a ensayos clínicos.

MODALIDADES DE ACCESO A LOS MEDICAMENTOS FUERA DE LA PRÁCTICA CLÍNICA HABITUAL



MODALIDADES DE ACCESO A LOS MEDICAMENTOS FUERA DE LA PRÁCTICA CLÍNICA HABITUAL



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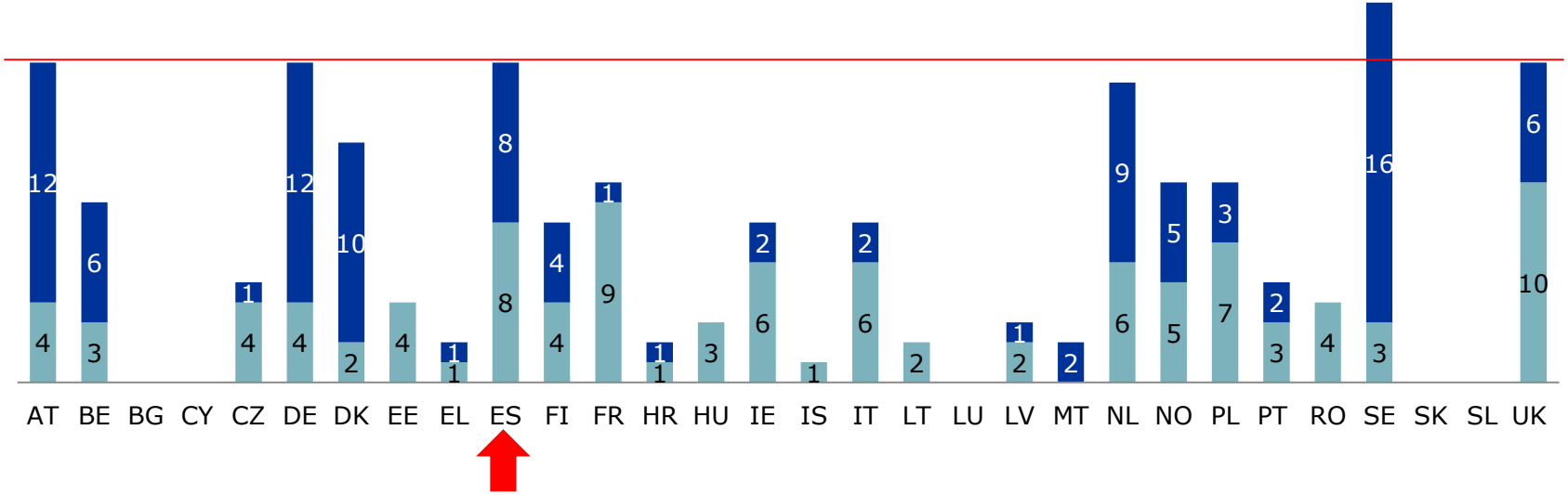
AEMPS

AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

Total CHMP Rapporteurship 2017



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oncology co-/rapp

GIOTRIF (afatinib)

ZYKADIA ceritinib 150 mg capsules

IMFINZI durvalumab

OPDIVO (nivolumab)

TAGRISSO osimertinib

Zytiga (abiraterone acetate)

Xtandi (enzalutamide) capsules

AXUMIN Fluciclovine F 18 Injection

OPDIVO (nivolumab)

Javlor vinflunina

OPDIVO (nivolumab) + YERVOY (ipilimumab)

KISQALI ribociclib

Rubraca (rucaparib) tablets

Yondelis (trabectedin)

Lartruvo (OLARATUMAB)

Lonsurf (trifluridine and tipiracil) tablets

glivec imatinib

Bosulif bosutinib 500 mg tablets

DARZALEX (daratumumab)

Imnovid (Pomalidomid)

Kyprolis (carfilzomib)

Vidaza azacitidine for injection

OPDIVO (nivolumab)

Zalmoxis

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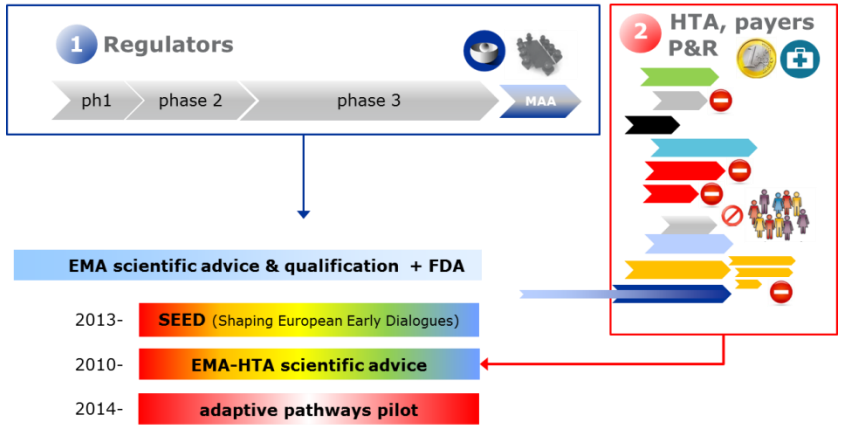
Oficina de apoyo a la INNOVACIÓN y CONOCIMIENTO sobre MEDICAMENTOS

–

Agencia Española de Medicamentos y Productos Sanitarios

health technology assessment (HTA)



2015/16/17 AEMPS involved in 3/2/9 procedures as HTA

eunethta
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

IPT – therapeutic positioning reports (REA)

dialogue regulators & HTAs & payers

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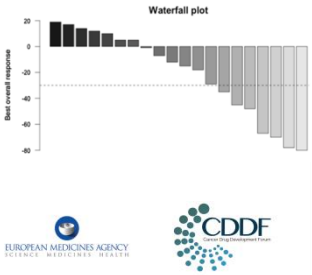
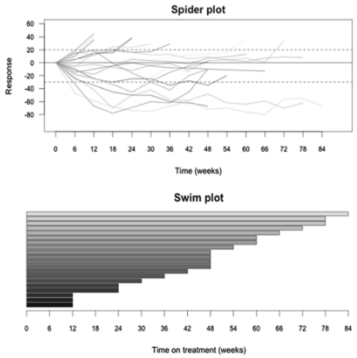
evidence interpretation

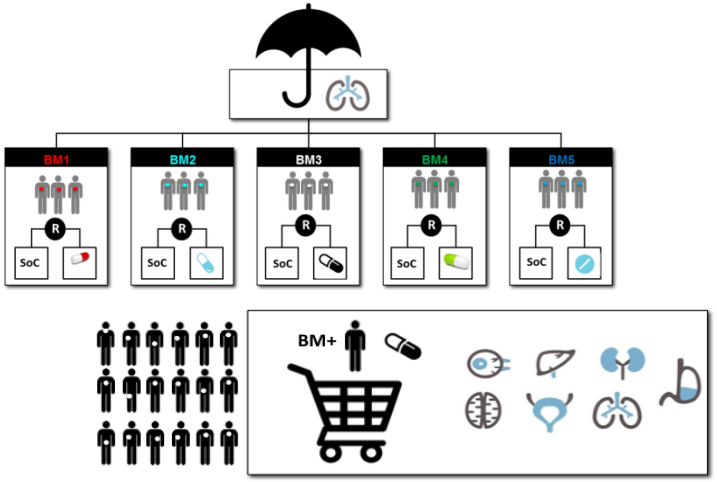


EMA-CDDF JOINT MEETING

CHALLENGES FOR THE APPROVAL OF ANTI-CANCER IMMUNOTHERAPEUTIC DRUGS

LONDON, UNITED KINGDOM – 4-5 FEBRUARY 2016





histology agnostic?

guidelines

Workshop on Site and Histology – Independent Indications in Oncology

Programme

14-15 December 2017

European Medicines Agency, London, United Kingdom

Meeting **room 2F**

early access to patients

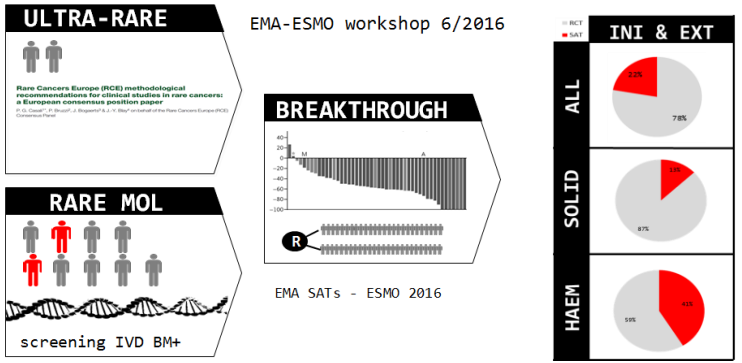
Annals of Oncology 27: 96–105, 2016
doi:10.1093/annonc/mdv506
Published online 20 October 2015

Early market access of cancer drugs in the EU

J. Martinalbo[1], D. Bowen[1], J. Camarero[2], M. Chapelin[1], P. Démolis[3], P. Foggi[4], B. Jonsson[5], J. Llinares[1], A. Moreau[3], D. O'Connor[6], J. Oliveira[7], S. Vamvakas[1] & F. Pignatti[1]*

glivec (imatinib) · DARZALEX (daratumumab) · TAGRISSO (osimertinib) · OPDIVO (nivolumab) + YERVOY (ipilimumab) · Zytiga (abiraterone acetate) · Xtandi (enzalutamide) capsules

non-RCT evidence?



Safe and Timely Access to Medicines for Patients (STAMP) EC Expert Group

national early access mechanisms
safety considerations (PRAC)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
PRIME – PRIORITY MEDICINES

involvement in program design

AEMPS as HTA

Thank you!

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Back-up slides

Designation of medicines for rare diseases (orphan designation)

→ Medicines to be developed for the diagnosis, prevention or treatment of rare diseases that are life-threatening or very serious. In the European Union (EU), a disease is defined as rare if it affects fewer than 5 in 10,0 EU

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The Committee for Orphan Medicinal Products (**COMP**) is the European Medicines Agency's (EMA) committee responsible for recommending orphan designation of medicines for rare diseases.

Pharmaceutical companies are unwilling to develop such medicinal products under normal market conditions, as the cost of bringing them to market would not be recovered by the expected sales of the products without incentives

incentives

Market exclusivity

For 10 years after the granting of a marketing authorisation (approval for sale), orphan medicinal products benefit from market exclusivity in the EU. During that period, directly competitive similar products cannot normally be placed on the market.

But…

- the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or;

- the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or;

- the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is **safer, more effective or otherwise clinically superior**.

Protocol assistance

Protocol assistance is available at a reduced charge for designated orphan medicines, linked to a fee-reduction scale that depends on the status of the sponsor. There is no restriction on the number of times a sponsor can request protocol assistance

Fee reductions

A special fund from the European Commission, agreed annually by the European Parliament, is used by the Agency to grant fee reductions. Reduction of fees will be considered for various centralised activities, including applications for marketing authorisation, inspections and protocol assistance. Additional fee reductions apply for small and medium-sized enterprises (SMEs).

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CHMP
RULES OF PROCEDURE

The Committee consists of **one member** appointed **by each** of the EU **Member States** (28+28)

The Committee shall also include **one member** appointed **by each** of the **EEA-EFTA States** (NO + IS)

The Committee may appoint up to **five co-opted members** chosen on the basis of their specific **scientific competence** (ES, UK, BE, CZ, DE)

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

agencia española de medicamentos y productos sanitarios

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Scientific opinions and recommendations

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

• The **quorum** required for the adoption of scientific opinions or recommendations by the Committee shall be reached when **two thirds of the total members** of the Committee eligible to vote are present.

• **Whenever possible**, scientific opinions or recommendations of the Committee shall be taken by **consensus**. If such a consensus cannot be reached, the scientific opinion **or** recommendation will be adopted if supported by an **absolute majority** of the members of the Committee.