EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Orphan medicines in EU

An overview

USA National Academies – Rare Disease Study

Presented by Steffen Thirstrup 4 Dec 2024
Chief Medical Officer

An agency of the European Union

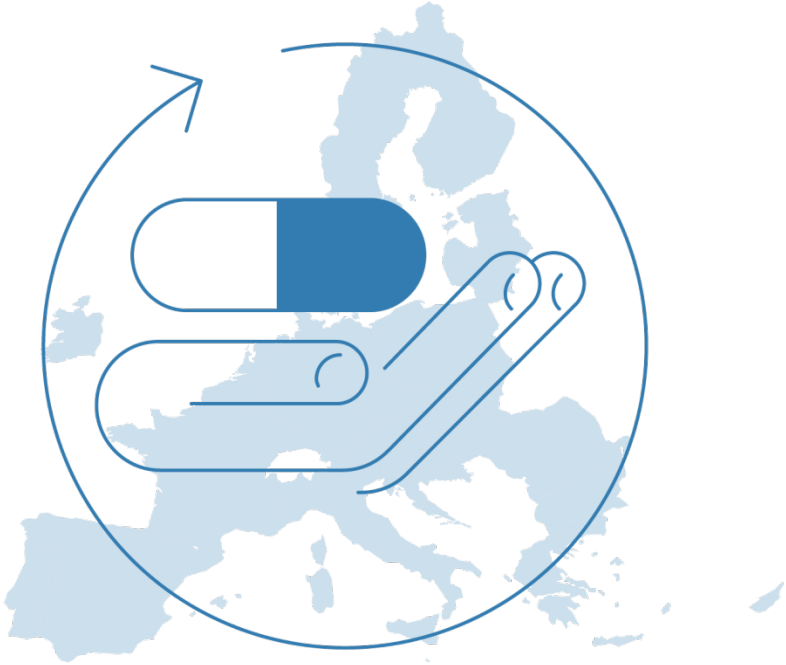
Disclaimer

The presenter does not have any conflict of interests.

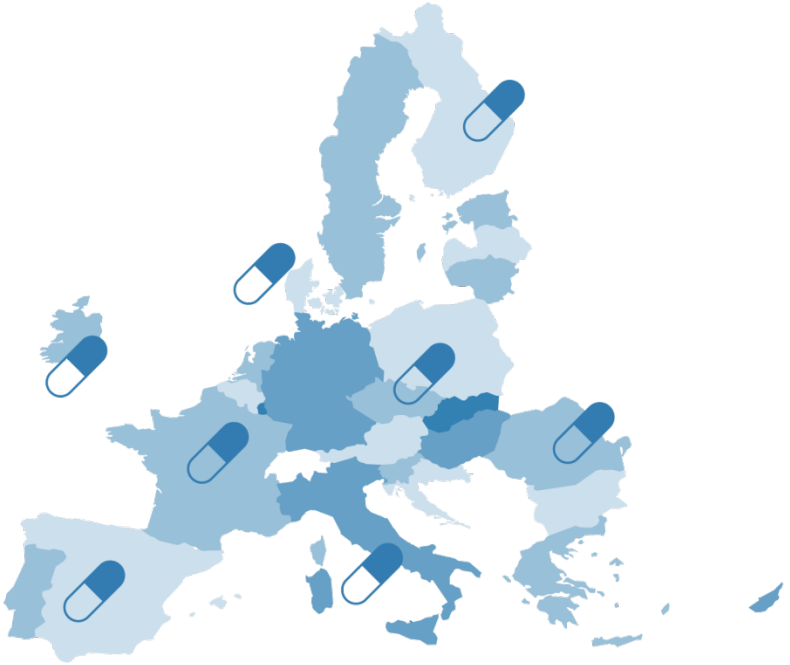
EU regulatory system - Overview

How are medicines approved?

Different authorisation routes: one set of common rules



Centralised procedure (via EMA)



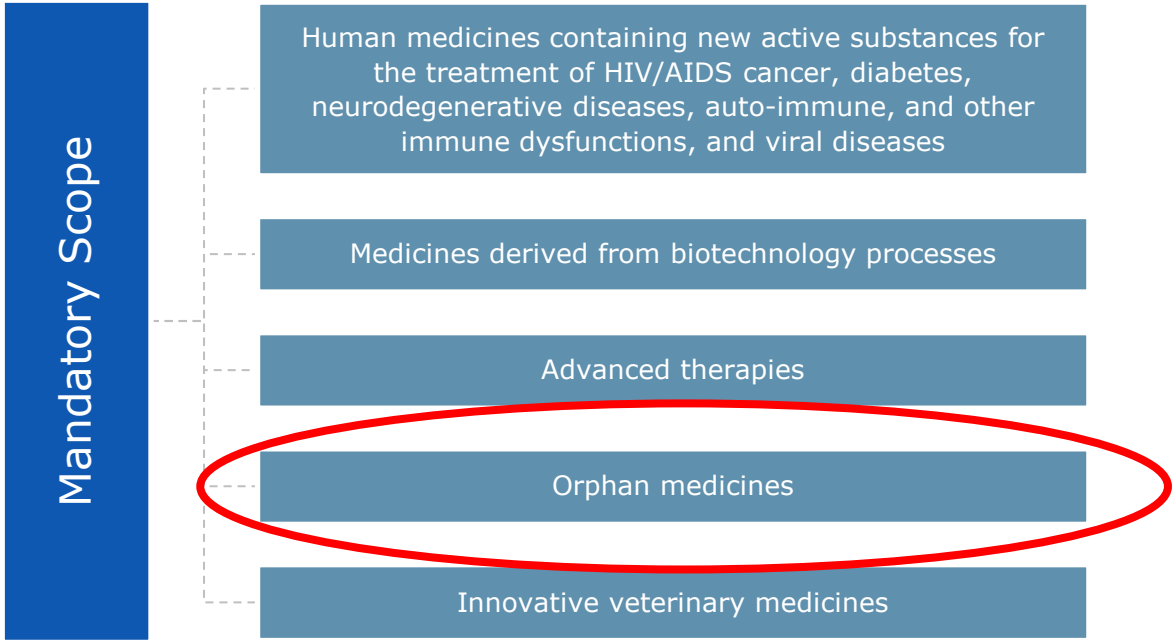
National procedures (via Member States)

Centralised Procedure

One application— one scientific evaluation— one marketing authorisation

- Dedicated to innovative products
- Mandatory for specific categories of products
- Opinion delivered by Scientific Committee
- Authorisation granted by the European Commission

Medicines approved through the centralised procedure



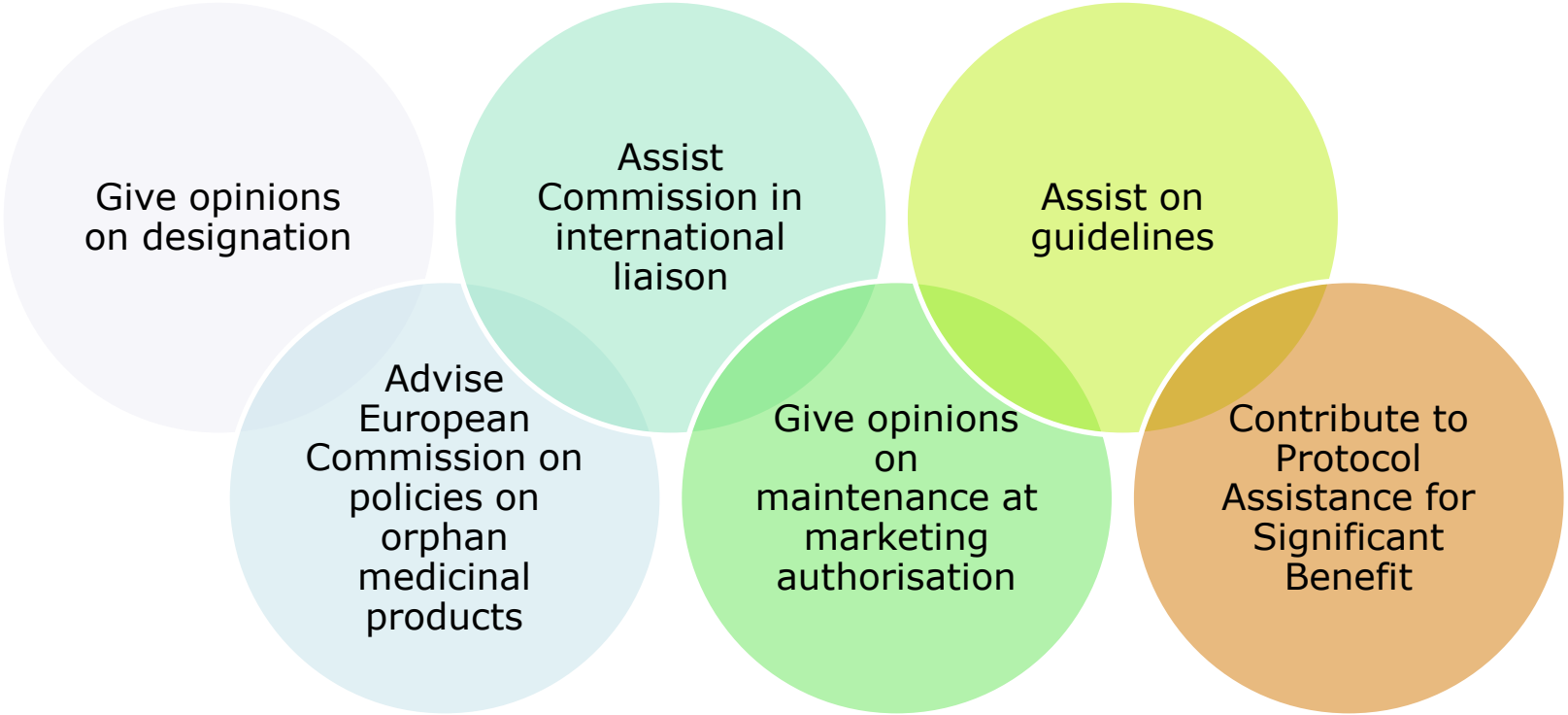
The EU centralised system – organisation

- Seven scientific committees and a number of working parties and related groups which conduct the scientific work of the EMA.

  - Committee for Medicinal Products for Human Use (CHMP)
  - Pharmacovigilance Risk Assessment Committee (PRAC)
  - Committee for Advanced Therapies (CAT)
  - **Committee for Orphan Medicinal Products (COMP)** (orphan status)
  - Paediatric Committee (PDCO) (paediatric plan)

- The committees, working parties and related groups are composed by **European experts** made available by National Competent Authorities.

COMP responsibilities



Orphan legislation and regulatory processes

Orphan Regulation in the EU

Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products of 16 December 1999

- Criteria for designation
- Committee (COMP)
- Procedure
- Incentives (market exclusivity)

Commission Regulation (EC) No 847/2000 of 27 April 2000

- laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and
- definitions of the concepts ‘similar medicinal product’ and ‘clinical superiority’

Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (Nov 2016)

European regulatory input along drug life cycle

Clinical development

Pharm | **Non-clinical** | **I** | **II** | **III** | **MAA** | **Post-mkt**

PhV

Assessment

Paediatric Investigation Plan

Orphan Drug Designation

Scientific Advice/Protocol Assistance

Orphan Maintenance

Designation criteria

RARITY (prevalence) / RETURN OF INVESTMENT (Art 3.1 (a) of 141/2000)

- Medical condition affecting not more than 5 in 10,000 in the Community (around 250,000 people)
- Without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment

SERIOUSNESS

- Life –threatening or chronically debilitating

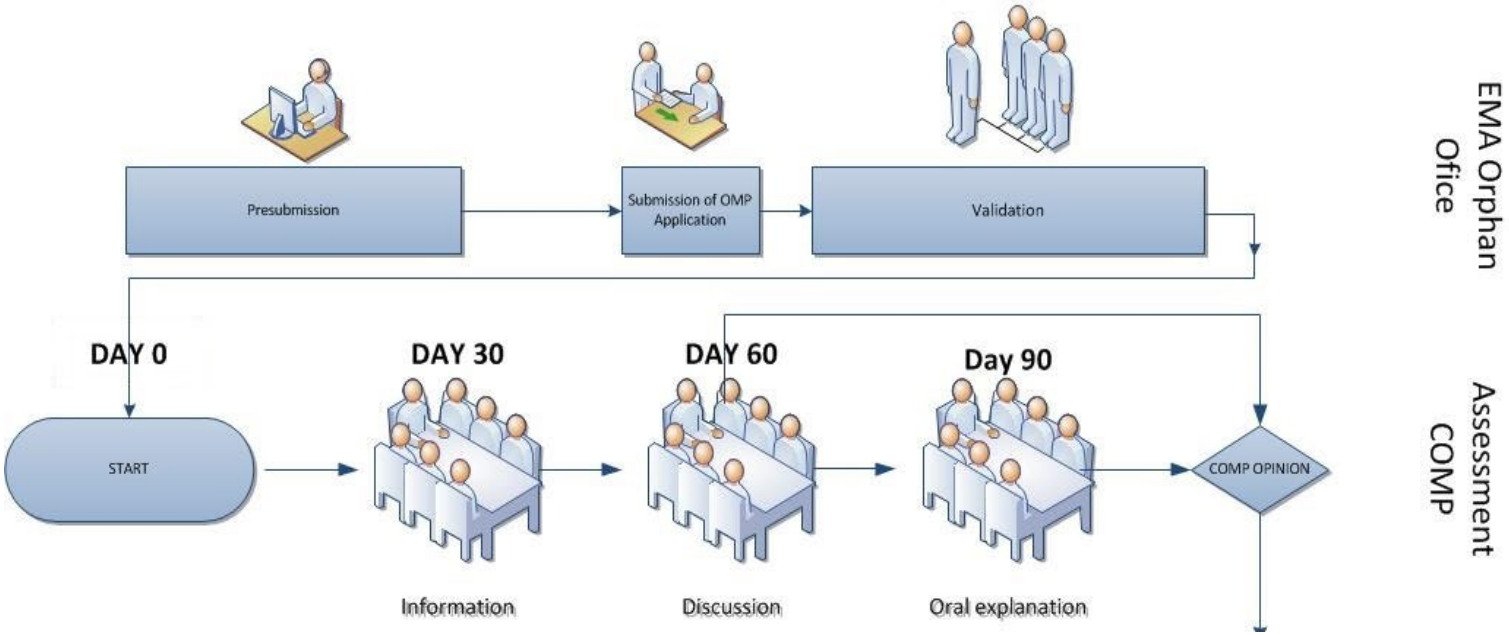
ALTERNATIVE METHODS AUTHORISED (Art 3.1(b)of 141/2000)

- If satisfactory method exist the sponsor should establish that the product will be of significant benefit

Incentives for orphan medicines

- Fee reduction / exemptions
  - Extended incentives for Small and Medium sized Enterprises (SMEs)
- 10-year market exclusivity (+ 2 if paediatric)
  - protection against similar products structure mech of action same indication
  - Three derogations: Sponsor's consent, Lack of supply, Clinical superiority
- Product development
  - *Protocol assistance* (~scientific advice), reduced fee
- Community marketing authorisation (all EU and EEA member states)

Designation process



European Commission decision

What is assessed?

At time of orphan designation

- The condition
- The chronically debilitating and life-threatening nature of the condition
- The intention to treat the condition (medical plausibility)
- The prevalence <5 in 10,000, see guidance on website
- The significant benefit (if applicable)

At time of marketing authorisation

- Quality / Safety / Efficacy
- Authorisation within designated condition
- The prevalence
- The significant benefit (if applicable)

Orphan condition

EC Guideline (ENTR/6283/00)

- Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome)
- Distinct: pathophysiological, histopathological, genetic subtype/genomic and clinical characteristics.
- Different severities- stages not acceptable
- Biomarkers currently not accepted
- Special considerations: subsetting (exclusive action), intersection, treatment modality

Significant benefit

- Unique to the European Orphan Regulation
- Defined as:

  - **a clinically relevant advantage**

  - **a major contribution to patient care**

Drug Discovery Today • Volume 00, Number 00 • November 2017

ELSEVIER

Teaser An analysis of the scientific grounds of the significant benefit as per the Regulation, supporting the added value for patients of those orphan medicinal pro demonstrate to be of significa

Demonstrating significant benefit of orphan medicines: analysis of 15 years of experience in Europe

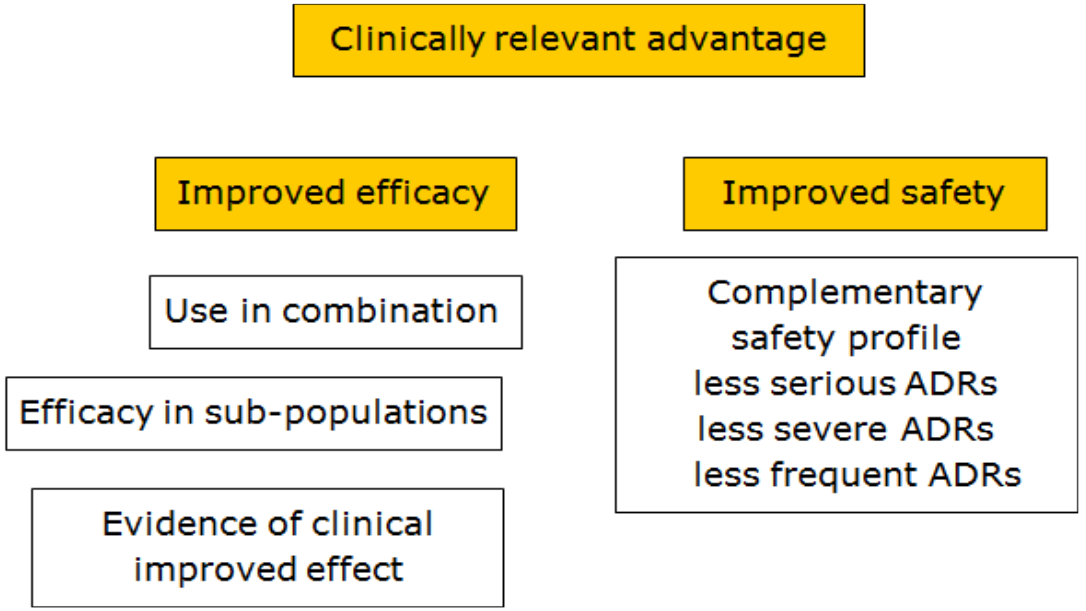
Laura Fregonese[1], Lesley Greene[2], Matthias Hofer[1], Armando Magrelli[3], Frauke Naumann-Winter[4], Kristina Larsson[1], Maria Sheean[1], Violeta Stoyanova-Beninska[5], Stelios Tsigkos[1], Kerstin Westermark[6] and Bruno Sepodes[7]

Laura Fregonese, MD PhD MS
Scientific Officer working in the O
Office at the European Medicines
specialist in clinical immunology a
medicine. She is the lead for projec
benefit of orphan medicines. Befo
she was involved as an academic
EU Rare Diseases Task Force in th
policies in the field of rare diseas
European Commission Communi
diseases: Europe's challenges and

Clinically relevant advantage

- legal definition: "*clinically relevant advantage*" translated into operational definition:

- "A **relevant clinical benefit** (in relation to all methods authorised for the condition) where there is a reasonable probability that the patient will actually experience this benefit"

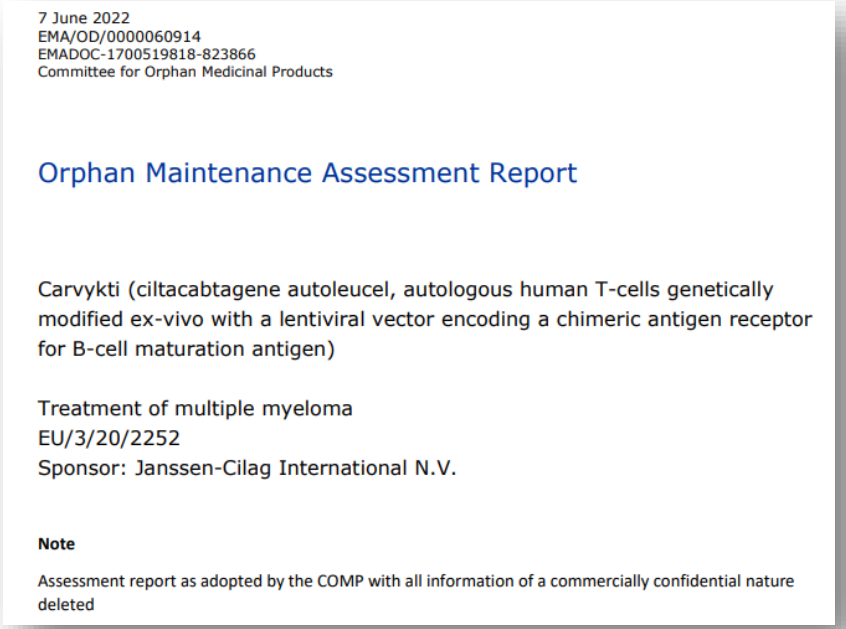


Clinically relevant advantage example

Carvykti for treatment of multiple myeloma:

"**improved and sustained** complete response rates after treatment with Carvykti **as compared to** Abecma in adult patients with relapsed and refractory multiple myeloma"

Based on indirect comparisons.



7 June 2022
EMA/OD/0000060914
EMADOC-1700519818-823866
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Carvykti (ciltacabtagene autoleucel, autologous human T-cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor for B-cell maturation antigen)

Treatment of multiple myeloma
EU/3/20/2252
Sponsor: Janssen-Cilag International N.V.

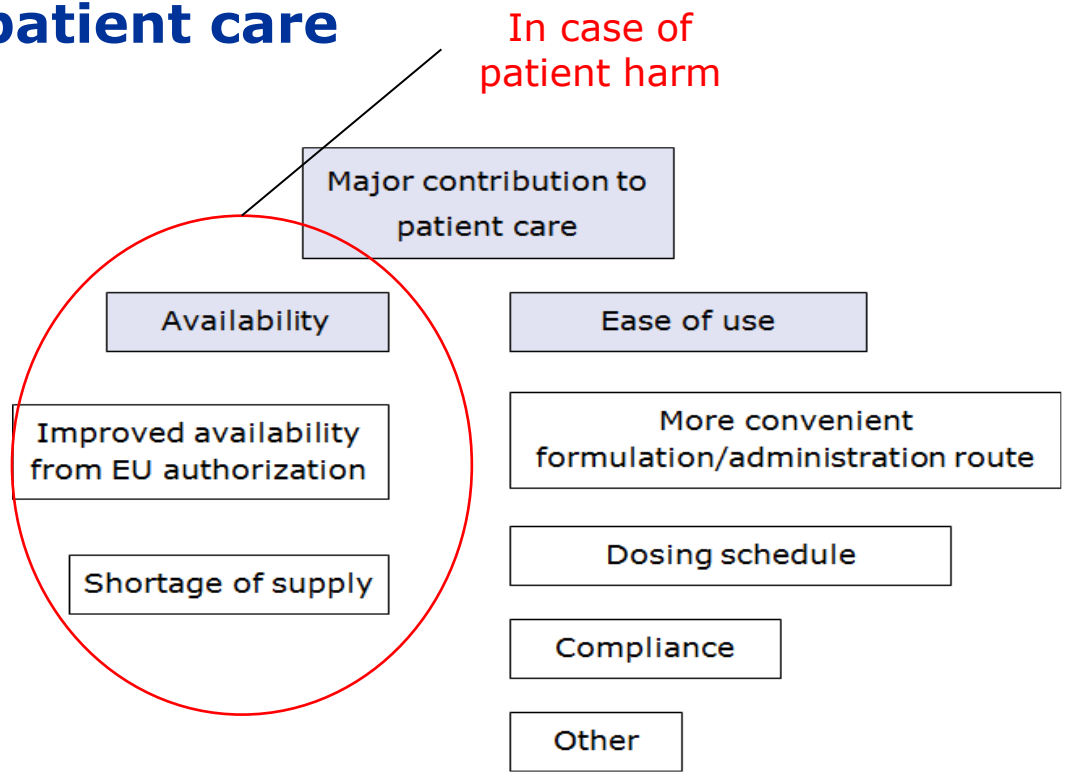
Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

Major contribution to patient care

Theoretical examples

- pills vs. injection (but not 3 pills a day vs 1 injection per month)
  - Ready to inject vs need to reconstitute (sterile)
- Easy to carry (e.g. not requiring storage in the fridge)



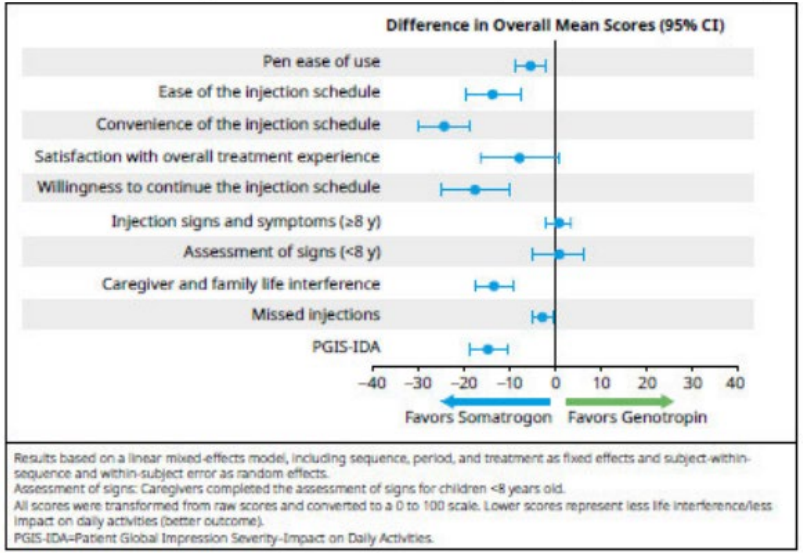
Major contribution to patient care example

Ngenla for treatment of growth hormone deficiency:

"treatment satisfaction data from a specifically designed study demonstrated that the **treatment burden** for patients and carers was reduced for somatrogon **as compared to** the somatropin control"

Direct comparison

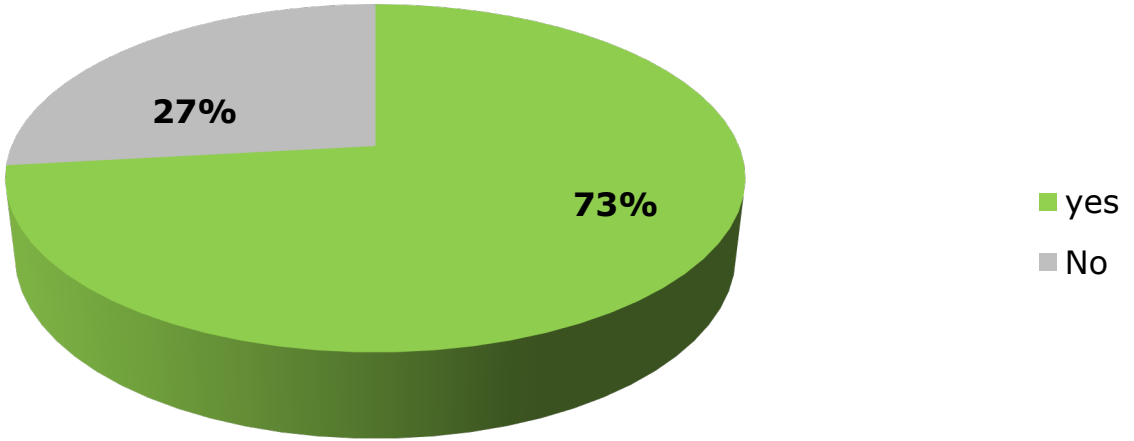
Figure 2. Patient and Caregiver Assessments of Treatment Experience (DCOA 1 and PGIS-IDA)



Results based on a linear mixed-effects model, including sequence, period, and treatment as fixed effects and subject-within-sequence and within-subject error as random effects.
Assessment of signs: Caregivers completed the assessment of signs for children <8 years old.
All scores were transformed from raw scores and converted to a 0 to 100 scale. Lower scores represent less life interference/less impact on daily activities (better outcome).
PGIS-IDA=Patient Global Impression Severity-Impact on Daily Activities.

Source: Maniatis et al. 2021, Figure 2.

Majority of products are designated and authorised with significant benefit



Orphanisation?

Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03)

- Justification for restricting to a subset of patients needed
  - Should be a recognisable clinical entity
  - Product should essential be ineffective in other/larger subsets of the condition

- *Significant benefit* cannot be claimed on:
  - Alternative mode of action *per se*
  - Increase in supply/availability due to shortage of existing products
  - Enhancement of pharmaceutical quality
  - ….

Negative opinion on orphan designation - Examples

- Non-small cell lung cancer with EGFR
  - Overlapping with NSCLC
- Intracerebral haemorrhage
- Non-traumatic subarachnoid haemorrhage
  - But does not affect a distinct subset of patients with stroke
- Poisoning by local anaesthetics
  - Not a distinct recognisable medical entity
- Uraemic pruritus
  - Not a distinct recognisable medical entity with signs/symptoms different from pruritus caused by other conditions

Science is dynamic


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 January 2023
EMADOC-628903358-34665
European Medicines Agency

Statement on the amended policy on orphan designations for inherited retinal dystrophies

Grouping for inherited retinal diseases for the purpose of orphan designation

1. Non-syndromic IRD
    - *1.1. Cone-dominant phenotype**
    - *1.2. Rod-dominant phenotype*
    - *1.3. Macular dystrophy*
2. Syndromic IRD
    - *2.1. Cone-dominant phenotype*
    - *2.2. Rod-dominant phenotype*
    - *2.3. Macular dystrophy*
3. Inherited choroidal dystrophies
4. Hereditary vitreoretinopathies

* Phenotypes include inherited pathological dysfunction as well as inherited progressive degenerations

Statement on the amended policy on orphan designations for inherited retinal dystrophies (europa.eu)

Marketing Authorisation and Maintenance of Orphan Designation

Authorisation of an orphan drug

- Based on same standards as for non orphan products (quality / safety / efficacy)
- Authorisation only centralised procedure
- CHMP responsible for assessment
- Authorisation within designated condition
- More than one designation possible per product (independent incentives)

Authorisation of an orphan drug – maintenance of the status

The sponsor is requested to submit a report on the maintenance of ODD criteria.

Guidance on the submission of this report in the pre-submission mtg for MAA.

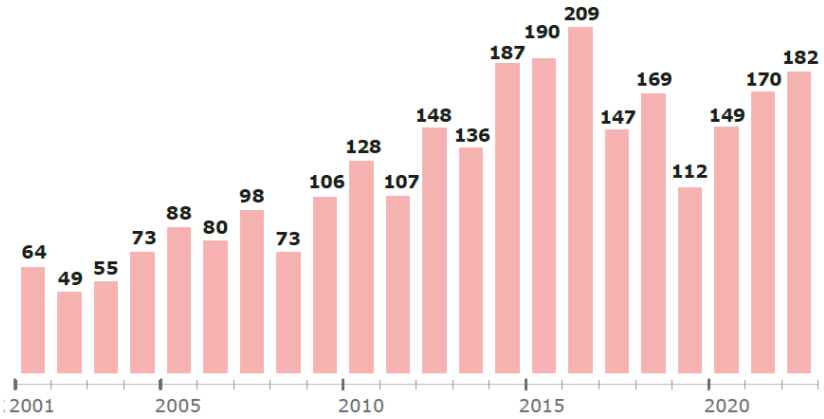
COMP re-evaluates the fulfilment of the criteria in parallel with the MA assessment, if doubt the sponsor will be invited for an oral hearing.

Opinion by COMP if the product should be removed or not from the Community Register

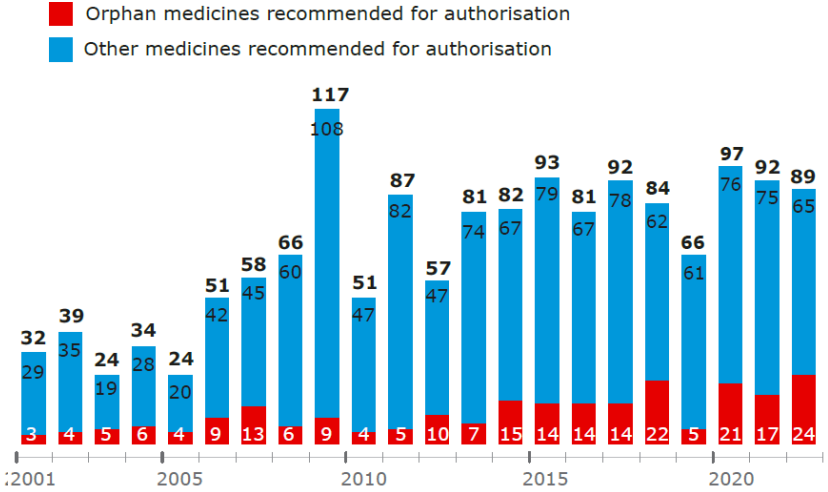
over **2730** medicines with orphan designation

over **230** orphan medicines authorised in the EU

Number of medicines that have received an orphan designation (2001-2022)



Number of orphan medicines recommended for authorisation (2001-2022)



www.ema.europa.eu

ORPHAN MEDICINAL PRODUCT DESIGNATION

Overview of orphan marketing authorisations granted to date

231 initial marketing authorisations granted

46 extensions of indication

- **141 active initial authorisations**
- **27 active extensions of indication**
- **27 withdrawals** from the register of orphan medicinal products (including 11 ext. of indication)
- **12 withdrawals** from register medicinal products human use/ orphan status expired
- **1 revoked** from register medicinal products human use/ orphan status expired
- **61 removals of initial MAA** from register after expire of the market exclusivity period plus **8 removals of extensions of indication**

Orphan drug statistics (data cut 28 Nov 2023)

- 142 currently active MAs
  - 98 full approvals
  - 26 conditional approvals
  - 18 approvals under exceptional circumstances
- 17 Refused MAs
- 72 Withdrawn MAs

EU orphan drugs approved *under exceptional circumstances*

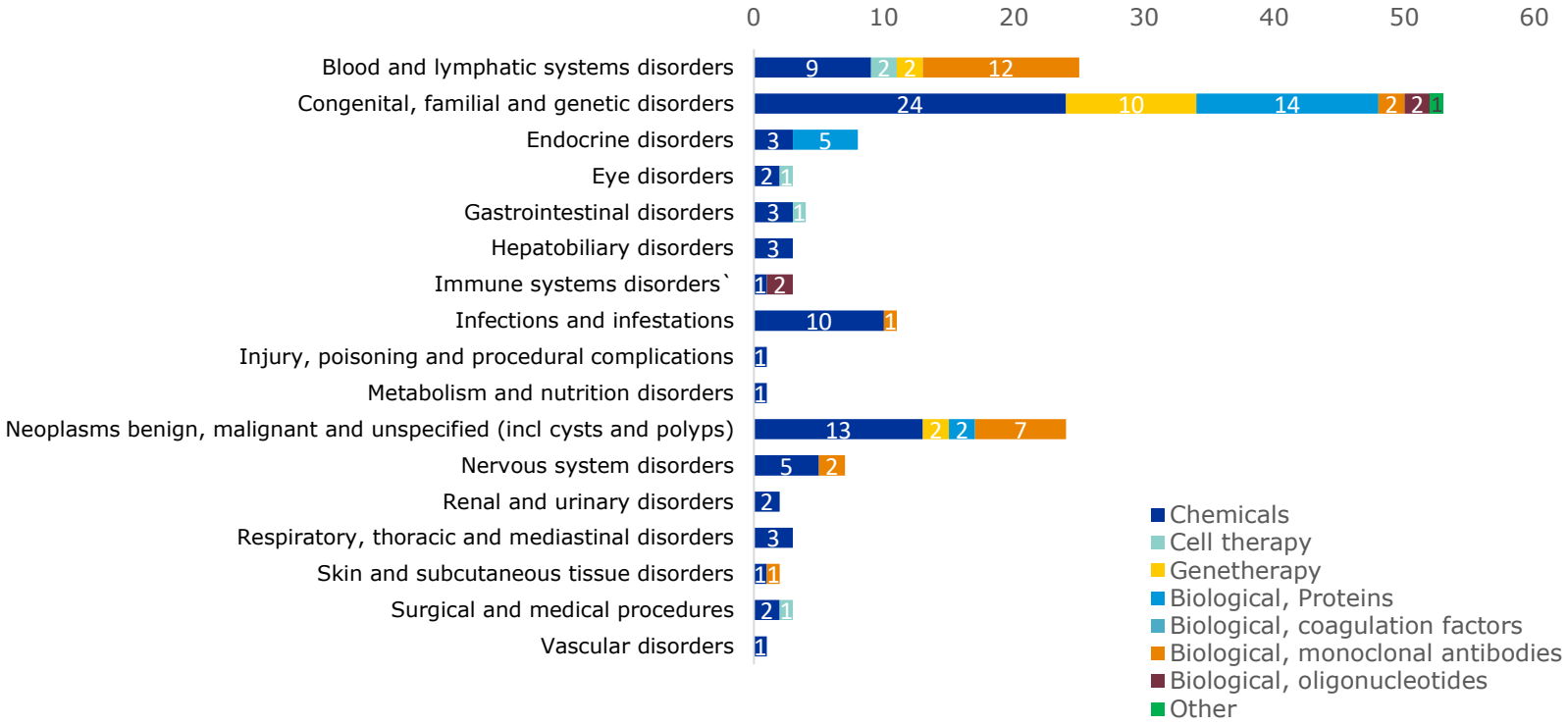
Medicine name	Therapeutic area	International non-proprietary name (INN) / common name
Livmarli	Alagille Syndrome	Maralixibat chloride
Zokinvy	Progeria; Laminopathies	lonafarnib
Raxone	Optic Atrophy, Hereditary, Leber	idebenone
Qarziba (previously Dinutuximab beta EUSA and Dinutuximab beta Apeiron)	Neuroblastoma	dinutuximab beta
Myalepta	Lipodystrophy, Familial Partial	metreleptin
Vyndaqel	Amyloidosis	tafamidis
Chenodeoxycholic acid Leadiant (previously known as Chenodeoxycholic acid sigma-tau)	Xanthomatosis, Cerebrotendinous; Metabolism, Inborn Errors	chenodeoxycholic acid
Mepsevii	Mucopolysaccharidosis VII	vestronidase alfa
Bylvay	Cholestasis, Intrahepatic	odevixibat
Upstaza	Amino Acid Metabolism, Inborn Errors	eladocagene exuparvovec
Elzonris	Lymphoma	tagraxofusp
Ebvallo	Lymphoproliferative Disorders	tabelecleucel
Lamzede	alpha-Mannosidosis	velmanase alfa
Strensiq	Hypophosphatasia	asfotase alfa
Nyxthracis (previously Obiltoxaximab SFL)	Anthrax	obiltoxaximab
Scenesse	Protoporphyria, Erythropoietic	afamelanotide
Brineura	Neuronal Ceroid-Lipofuscinoses	cerliponase alfa
Voraxaze	Metabolic Side Effects of Drugs and Substances	glucarpidase

EU orphan drugs *conditionally approved*

Medicine name	Therapeutic area	International non-proprietary name (INN) / common name
Holoclar	Stem Cell Transplantation; Corneal Diseases	ex vivo expanded autologous human corneal epithelial cells containing stem cells
Talvey	Multiple Myeloma	talquetamab
Lunsumio	Lymphoma, Follicular	mosunetuzumab
Minjuvi	Lymphoma, Large B-Cell, Diffuse	tafasitamab
Blenrep	Multiple Myeloma	belantamab mafodotin
Zolgensma	Muscular Atrophy, Spinal	onasemnogene abeparvovec
Tepkinly	Lymphoma, Large B-Cell, Diffuse	epcoritamab
Roctavian		Valoctocogene roxaparvovec
Pemazyre	Cholangiocarcinoma	pemigatinib
Natpar	Hypoparathyroidism	parathyroid hormone
Kinpeygo	Glomerulonephritis, IGA	budesonide
Deltyba	Tuberculosis, Multidrug-Resistant	delamanid
Idefirix	Desensitization, Immunologic; Kidney Transplantation	imlifidase
Abecma	Multiple Myeloma; Neoplasms; Cancer; Neoplasms, Plasma Cell; Hemostatic Disorders; Vascular Diseases; Cardiovascular Diseases; Paraproteinemias; Blood Protein Disorders; Hematologic Diseases; Hemic and Lymphatic Diseases; Hemorrhagic Disorders; Infectious Mononucleosis; Lymphoproliferative Disorders; Immunoproliferative Disorders; Immune System Diseases	idecabtagene vicleucel
Carvykti	Multiple Myeloma	ciltacabtagene autoleucel
Columvi	Lymphoma, Large B-Cell, Diffuse	glofitamab
Koselugo	Neurofibromatosis 1	selumetinib
Ayvakyt	Gastrointestinal Stromal Tumors	avapritinib
Hemgenix	Hemophilia B	etranacogene dezaparvovec
Ocaliva	Liver Cirrhosis, Biliary	obeticholic acid
Dovprela (previously Pretomanid FGK)	Tuberculosis, Multidrug-Resistant	pretomanid
Sirturo	Tuberculosis, Multidrug-Resistant	bedaquiline
Translarna	Muscular Dystrophy, Duchenne	ataluren
Polivy	Lymphoma, B-Cell	polatuzumab vedotin
Tecartus	Lymphoma, Mantle-Cell	Brexucabtagene autoleucel
Waylivra	Hyperlipoproteinemia Type I	volanesorsen

ORPHAN MEDICINAL PRODUCT DESIGNATION

Authorisations by type of product



Transparency and International Collaboration

Communication

- EMA orphan designation website
  - Q&A (general public)
  - Guidance documents
- COMP minutes
- Scientific publications

Rare diseases, orphan medicines

Getting the facts straight

Communication cont.

Orphan Maintenance Assessment Report (OMAR) - published with EPAR

- Published for all positive and negative COMP opinions, as well as removals.
- They describe the orphan condition and its seriousness, the spread of the condition at the time of maintenance of the designation, and, if applicable, the significant benefit over already authorised medicines.


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 July 2018
EMA/462162/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

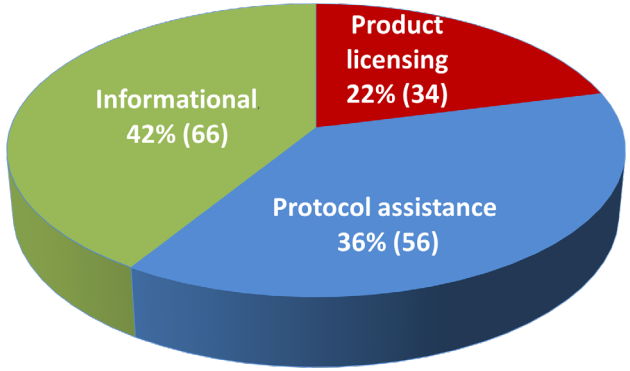
Myalepta (metreleptin)
Sponsor: Aegerion Pharmaceuticals B.V.

International collaboration

Orphan Cluster with FDA on orphan designations

Rare Diseases Cluster (FDA, Health Canada, Japan (observer))

- Cluster Primary Goal: To conduct joint meetings that facilitate alignment between regulatory agencies about scientific advice, licensing/marketing, and review to accelerate drug development in rare diseases.
- Overall, a total of 156 topics have been discussed at the Rare Diseases Cluster between September 2016 – June 2022.



Any questions?

Further information

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