



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Orphan designation in the EU

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Workshop with Japanese Pharmaceutical Industry

19 September 2013, London

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Head of Product Development Scientific Support

An agency of the European Union





# Outline

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Overview orphan designation

Procedure and criteria

- Definition of a medical entity
- Significant benefit

Outcomes



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## Overview orphan designation

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### Outcomes



# Objective of the Regulation

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provide incentives  
that stimulate  
research and  
development (push)

modify market  
conditions (pull)

Set up system of  
recognition orphan  
drugs entitled for  
incentives



## Legal references in the EU

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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

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

Commission communication July 2003 (2003/C 178/02)

Commission communication on Art 8(1) and (3) (C(2008) 4077)



# Main characteristics orphan designation

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- For medicinal products for human use
- For treatment, prevention or diagnosis of a rare disease
- Procedure free of charge
- Can be requested at any stage of development
- Sponsor can be either company or individual
  - Established in the Community (EU, Ice, Liech, Nor)
- European Commission Decision gives access to incentives



# Incentives

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Protocol assistance:  
Scientific Advice with  
significant fee  
reductions

Priority Access  
to Parallel  
Scientific Advice  
with FDA

Fee reduction /  
exemption at Marketing  
Authorisation Stage  
(annually reviewed)

Extended incentives for  
small and medium  
sized enterprises  
(SMEs)

Market exclusivity (10  
years)

(+ 2 if paediatric  
indication – completion  
investigation plan)

Automatic access to EU  
wide marketing  
authorisation



# Protocol assistance

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Simple fast procedure: 70 days including face to face meeting

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Scientific advice is the forum to agree the methodological approach in quality, non-clinical and clinical

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Quality: comparability and potency assays

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Non-clinical: relevance of animal models for pharmacology and toxicology

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Clinical: milestones of study design, including e.g. non-feasibility to conduct a comparative trial

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Significant Benefit



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# Designation criteria

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## **RARITY (prevalence) / RETURN OF INVESTMENT**

Medical condition affecting not more than 5 in 10,000 persons in the Community (around 250,000)

Without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment

## **SERIOUSNESS**

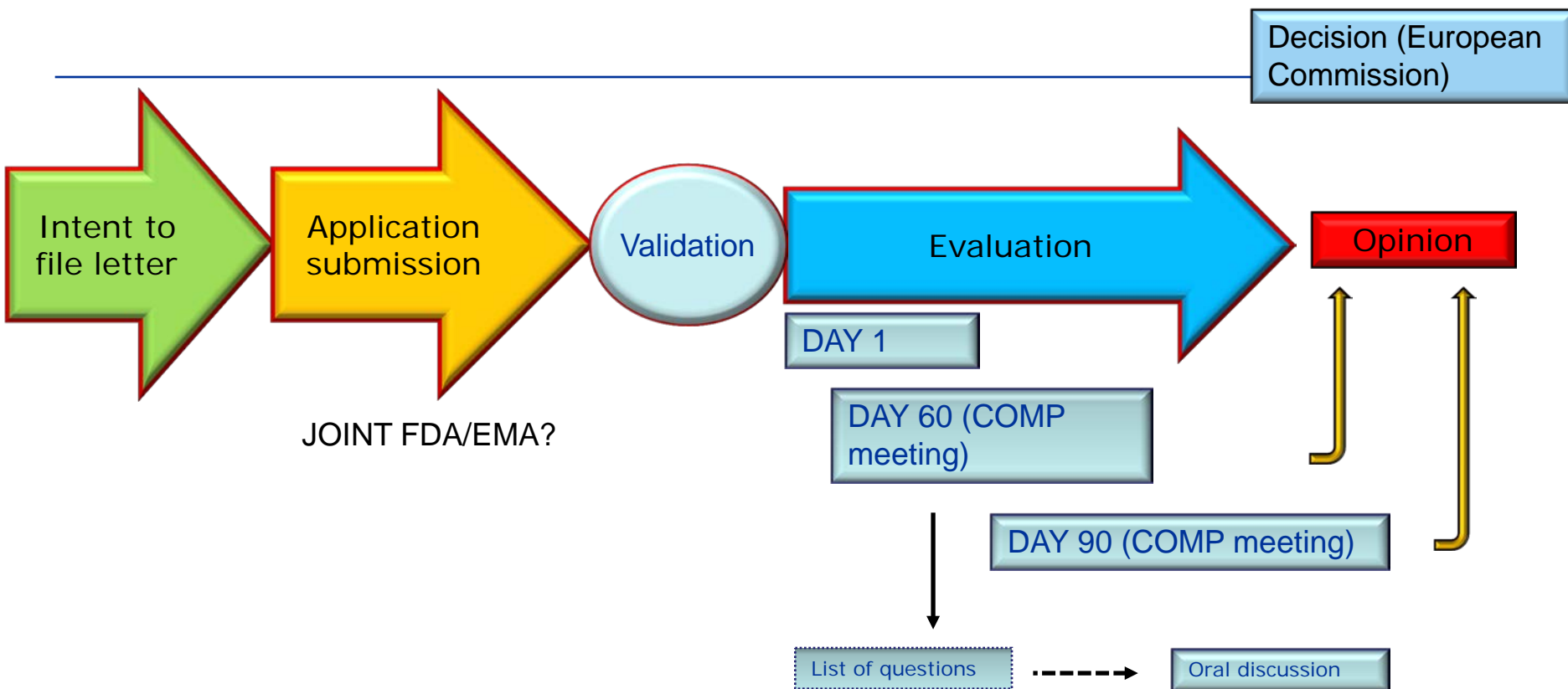
Life –threatening or chronically debilitating

## **ALTERNATIVE METHODS AUTHORISED**

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



# The designation process in the EU





# Committee for Orphan Medicines (COMP)

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1 elected Chair (Prof Bruno Sepodes)

Vice chair: Lesley Greene (Patient Rep)

1 Representative per Member State

3 Patients' Representatives appointed by Eur Commission

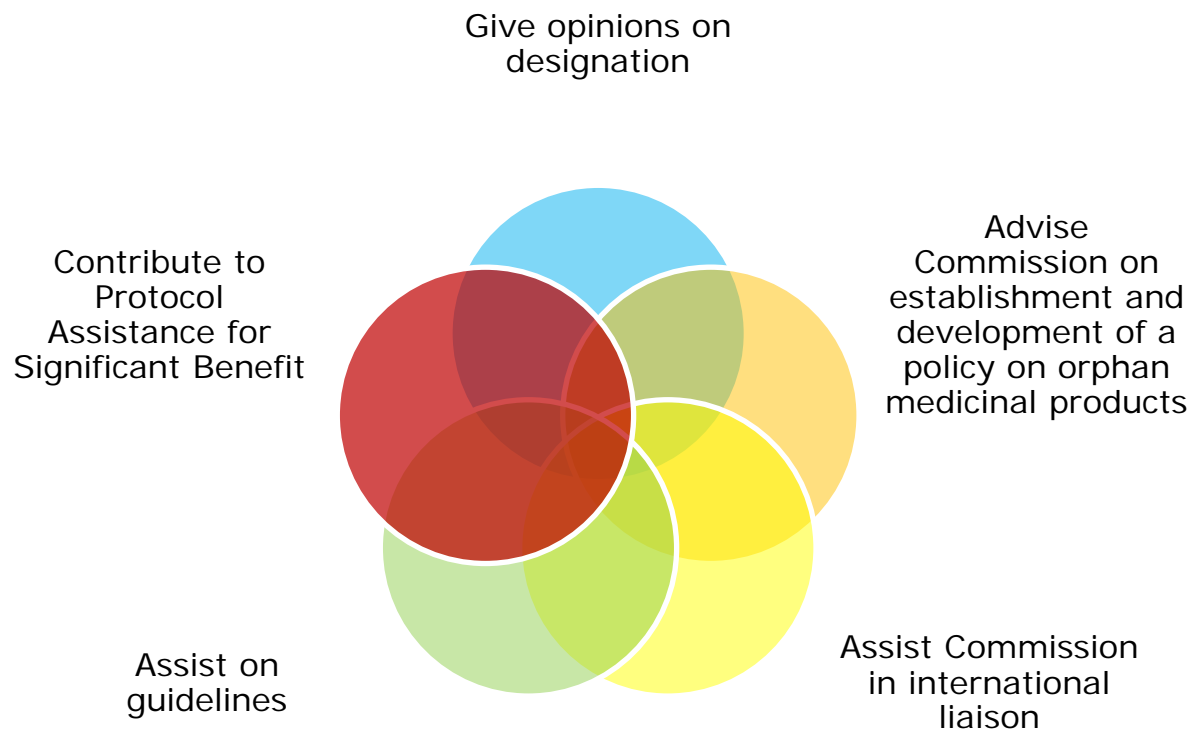
3 Members appointed by Eur Commission on proposal from Agency

1 Member for Norway, and 1 for Iceland



# COMP responsibilities

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# Medical condition

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## EC Guideline (ENTR/6283/00)

- Definition:
  - 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)
- Development plausible based on pathogenesis and pharmacodynamics
- Distinct pathophysiology, histology, clinical presentation
- Different severities- stages not acceptable



## Accepting subsets?

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### Medically plausible subset:

Usually defined by characteristics of the drug that limit the use of the investigational medicinal product in only the subset of the patients with the disease:

- Subset is medically recognizable
- To restrict the use of the medicinal product in the population subset → scientific-based justification should be provided
- It is expected that the drug will not be effective/safe for the rest of patients population not included in the subset



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# Significant benefit

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Significant benefit: “A clinically relevant advantage or a major contribution to patient care”

- Based on assumptions at the time of orphan designation
- Significant benefit over authorised products (=satisfactory methods)
- COMP to assess whether or not sign benefit assumptions are supported by available data/evidence supplied by applicant
- Sign benefit to be confirmed prior to marketing authorisation to maintain orphan status
- Recommendation document on data for SB and plausibility



# Examples assumption for significant benefit

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Claims of better efficacy

Drug has a new mechanism of action

- Efficacy will have to be demonstrated
- Opens possibilities for drug combination

More convenient administration route (major contribution to patient care)

Better safety

- Most times complementary safety profile
- Weak assumption for justification of sign benefit (data to support?)



## More on significant benefit

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- Higher level of evidence required at time of marketing authorisation compared to time of designation (in line with stage of development)
- Comparative data may be necessary
- Claim on different mechanism of action should be accompanied by data on benefit
- Safety profile is usually characterised after the product is placed on the market



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Overview orphan designation

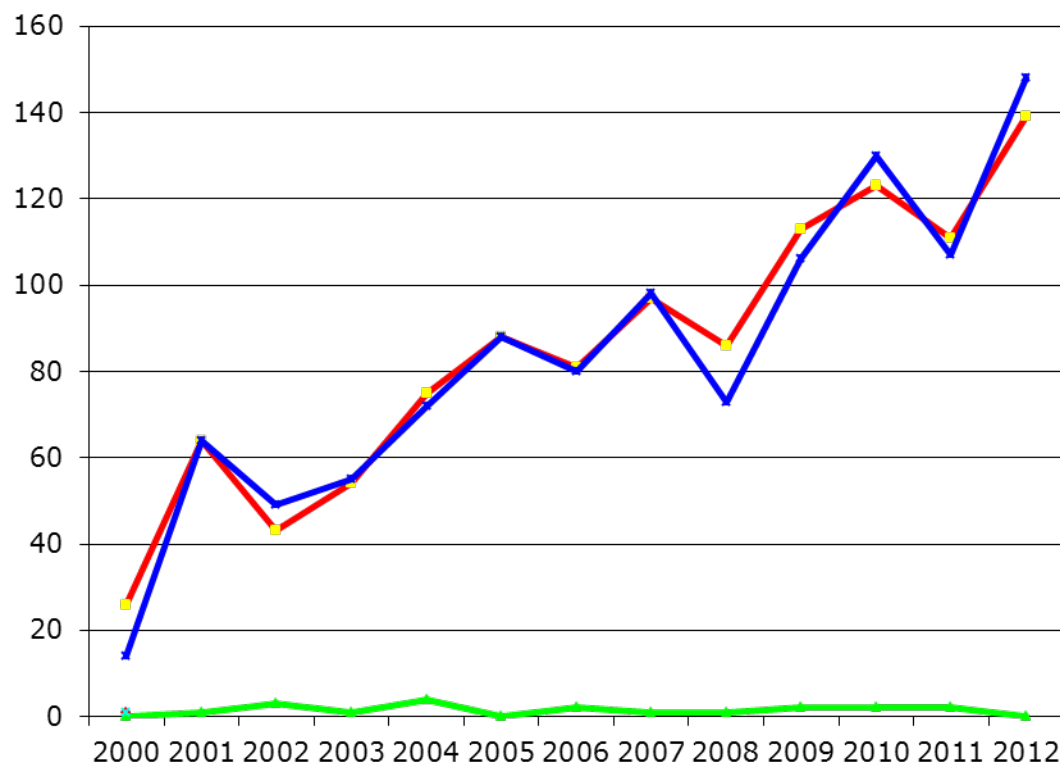
Procedure and criteria

- Definition of a medical entity
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# Evolution orphan designations in the EU



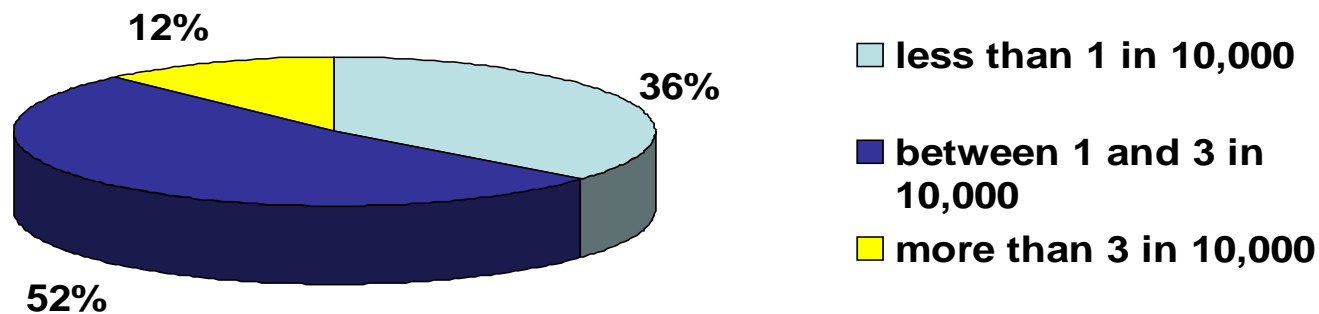
- Approx 70% success rate
- Re-submission possible and common

positive opinions      negative opinions      Commission decisions



# Designations per prevalence

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## Fee reductions

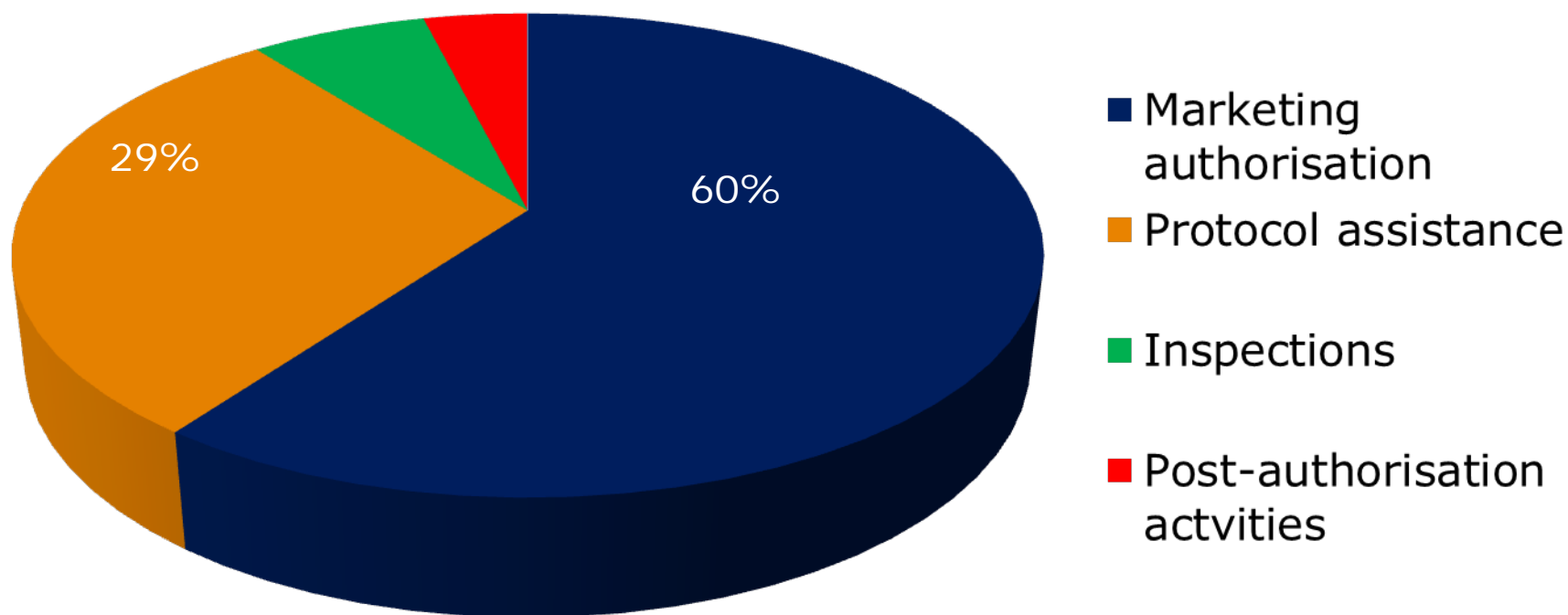
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- Annually EU allocated special fund to cover fee reductions (approx. 6 million Euro)
- EMA has consistently kept maximum coverage for SMEs
- Academia and SME in 79% development of advanced therapies
- Policy reviewed annually, needed revision in 2013 according to current budget



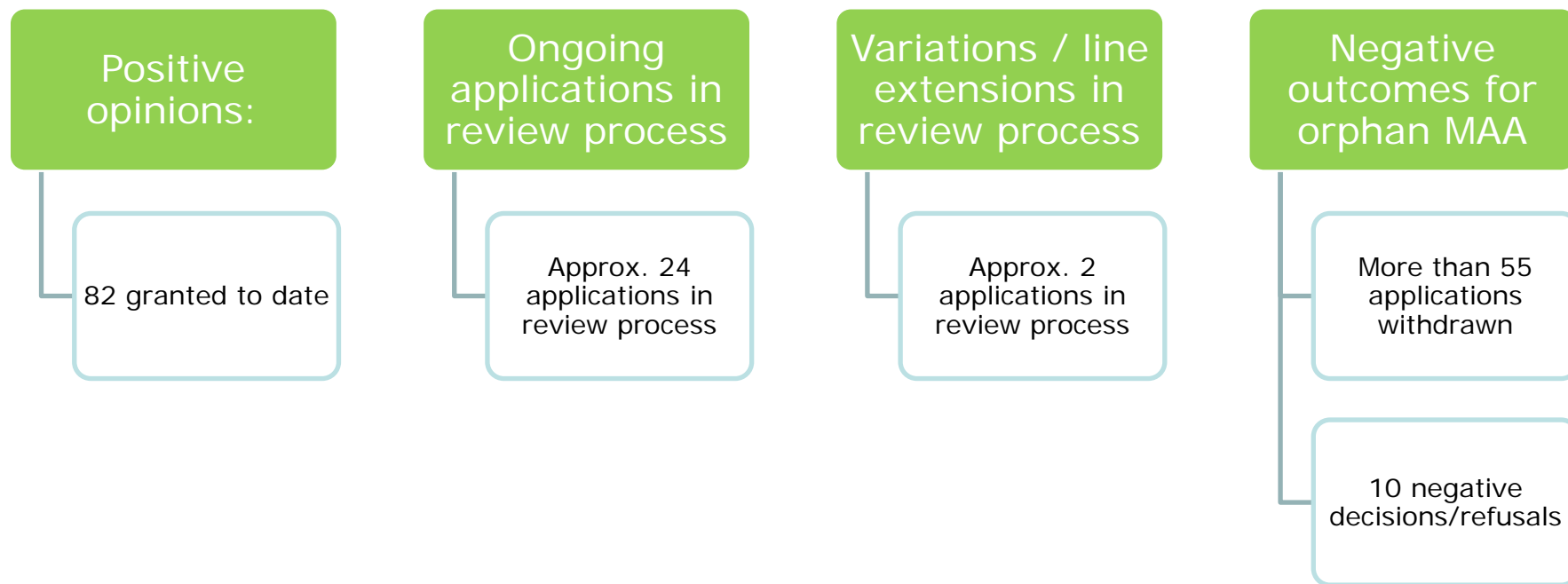
# Allocation funds for fee reductions (2012)

## Use EU fund





# Marketing authorisations





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Other activities



## What information is public today?

### Orphan designation

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- COMP monthly report (after opinion)
- EU Commission Register of orphan designated medicinal products (after decision)
- Public summary of positive/negative opinion for orphan designation (after decision)
- Position on the removal of a designated orphan medicinal product from the community register (COMP monthly report)
- Position on review of criteria for orphan designation at time of MA (from 2010)



# Information about review orphan status at time of authorisation

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Summary of COMP position on the review on web

Includes information on

- prevalence
- seriousness
- and significant benefit if applicable

Link to EPAR and viceversa

Publication since 2010



# Latest developments

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- Increasing dialogue between regulators and health technology assessment bodies: parallel EMA-HTA scientific advice / protocol assistance
- Strong EU and international support to research in rare diseases: next EU research program (Horizon 2020) and new International Consortium for Prioritisation of Research Funds (IRDiRC), a collective that aims to deliver 200 new therapies by 2020



European Medicines Agency - Human medicines - EU/3/05/267 - Windows Internet Explorer

http://www.ema.europa.eu/ema/index.jsp?url=pages/medicines/human/orphans/2009/11/human\_orphan\_000273.jsp&mid=WC0b01ac058001d12b

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Veterinary medicines  
Herbal medicines for human use

EU/3/05/267

Orphan designation Key facts Review of designation

Please note that this product was withdrawn from the Community Register of designated orphan medicinal products in July 2008 on request of the sponsor.

On 10 March 2005, orphan designation (EU/3/05/267) was granted by the European Commission to Pfizer Limited, United Kingdom, for (Z)-N-[2-(diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysuccinate for the treatment of malignant gastrointestinal stromal tumours.

Expand all items in this list

- What are malignant gastrointestinal stromal tumours?
- What is the estimated number of patients affected by the condition?
- What treatments are available?
- How is this medicine expected to work?
- What is the stage of development of this medicine?
- Opinions on orphan medicinal product designations are based on the following three criteria:

Name	Language	First published	Last updated
EU/3/05/267: Public summary of positive opinion for orphan designation of (Z)-N-[2-(Diethylamino)ethyl]-5-			

Sponsor's contact details:  
Pfizer Limited  
Ramsgate Road  
Sandwich  
Kent CT13 9NJ  
United Kingdom  
Telephone: +44 13 04 64 85 30  
Telefax: +44 13 04 65 50 47

Patients' associations contact points:  
The Association of European Cancer Leagues (ECL)  
c/o Belgian Federation against Cancer  
Chaussée de Louvain, 479  
B-1030 Brussels  
Belgium  
Telephone: +32 2 743 3705  
Telefax: +32 2 734 9250  
E-mail: chartmann@cancer.be

Ligue Nationale Contre le Cancer  
13 Av. de la Grande Armee  
75116 Paris  
France  
Telephone: +33 1 45 00 00 17  
Telefax: +33 1 45 00 63 06  
E-mail: ligue@ligue-cancer.net

Local intranet | Protected Mode: Off 125% 13:48 09/10/2012



# Many thanks

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any questions?

EMA website: <http://www.ema.europa.eu>



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See:

<http://www.emea.europa.eu/htms/technical/dmp/copyritel.htm>