EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Post Designation and Orphan Medicines

Outline

- Purpose of Regulation 141/2000
- Protocol assistance & Paediatric Investigational Plan
- Annual Reports
- Marketing authorisation

Purpose of the regulation

- to provide incentives for research, marketing and placing on the market designated orphan medicinal products
- to set up system for designation of orphan medicines

Activities after orphan designation

This section provides information on the incentives available to sponsors of medicines that have obtained orphan designation and the activities that take place after a designation has been granted.

Sponsors who obtain orphan designation benefit from a number of orphan incentives, including protocol assistance, a type of scientific advice specific for designated orphan medicines, and market exclusivity once the medicine is on the market. Fee reductions are also available depending on the status of the sponsor and the type of service required.

Sponsors must submit an annual report on development to the Agency summarising the status of development of the medicine.

Applications for **marketing authorisation** for designated orphan medicines are assessed by the Committee for Medicinal Products for Human Use (CHMP). Sponsors also need to submit an application for maintenance of the orphan designation in order to be eligible for the 10-year market exclusivity incentive. For more information, see marketing authorisation and market exclusivity.

Transfers of orphan designation from one sponsor to another are also possible. Transfers are free of charge.

Sponsors of medicines with orphan designation should also remember to apply for a **paediatric investigation plan**, deferral or waiver once phase-I clinical studies are complete. For more information, see paediatric medicine development.

More information

- Orphan incentives
- Annual report on development
- Marketing authorisation and market exclusivity
- Transfers of orphan designation

Related information

- Orphan designation
- Medicines for rare diseases: background information

Contact point:

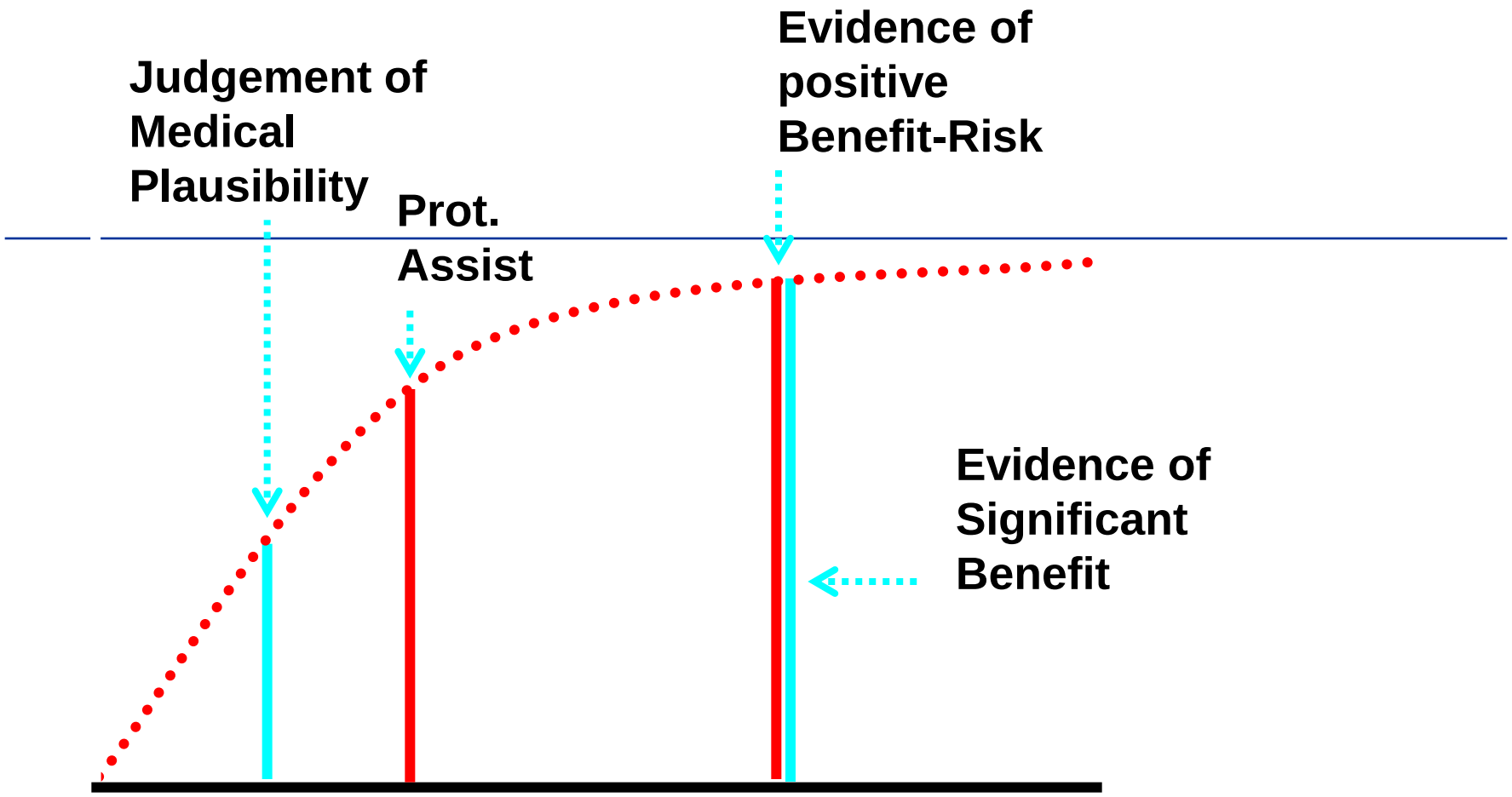
orphandrugs@ema.europa.eu

Post designation Regulatory Planning

- Companies who wish to obtain an Orphan Medicinal Designation need to factor specific post-designation incentives:
  - Which Committee does what?
  - Protocol Assistance/Scientific Advice why and when.
  - Paediatric Investigational Plan why and when.
  - Centralised MAA what are the needs and rewards.

Committee for orphan medicinal products (COMP)

COMP and CHMP roles

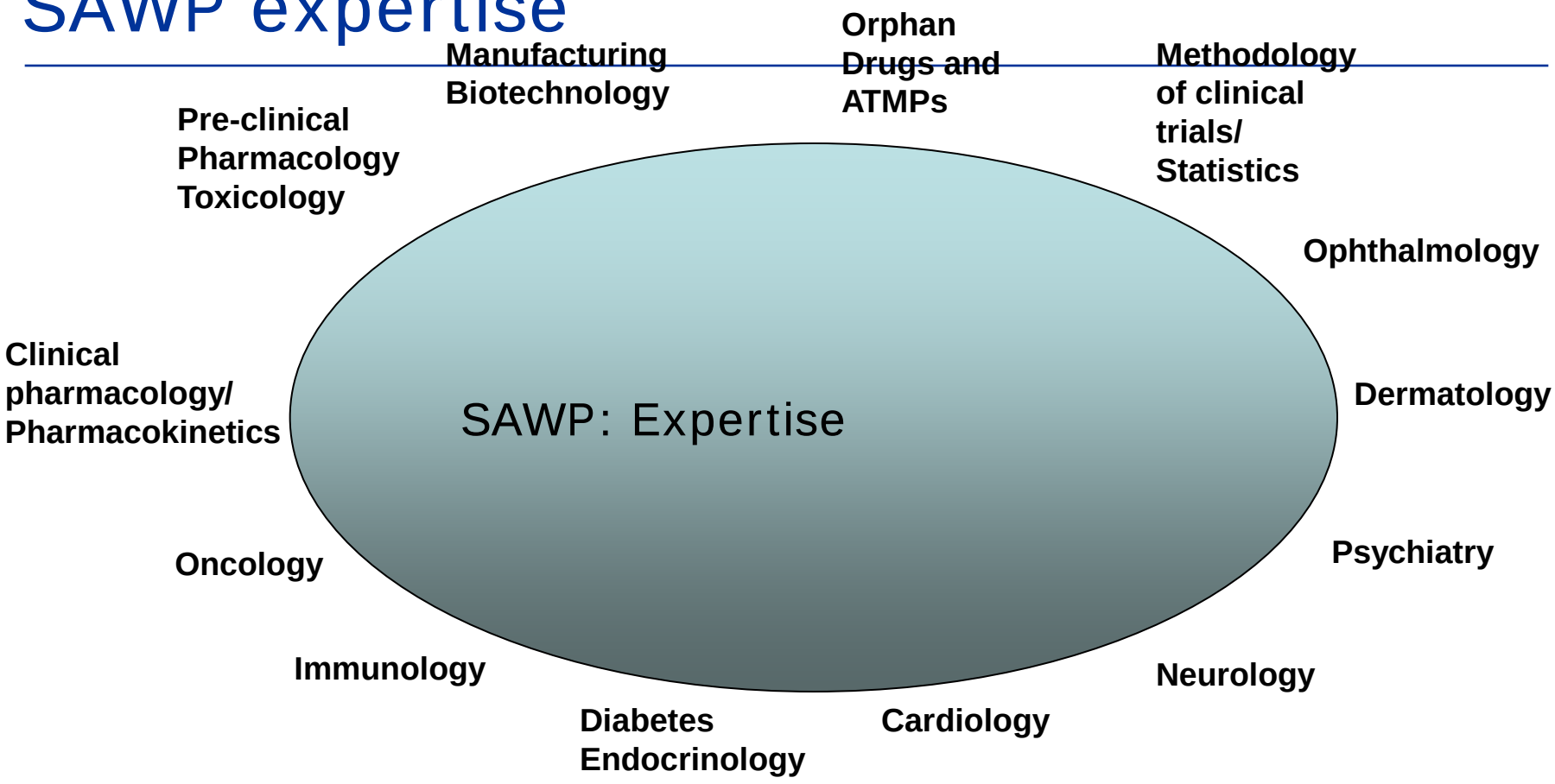


Protocol Assistance & Paediatric Investigational Plans

Protocol Assistance and SAWP

- For the sake of clarity protocol assistance is the samething as scientific advice and is a service offer by the Scientific Advice Working Party (SAWP).
- SAWP is made up of 30 members with different scientific disciplines who are selected for their expertise in either quality, non-clinical and clinical issues.
- SAWP is a voluntary fee paying service for all who wish to develop products for the purpose of obtaining an MAA.
- There is no limit to the number of times a company can come and it is not limited to certain phases of development like the FDA.

SAWP expertise



How SAWP functions.

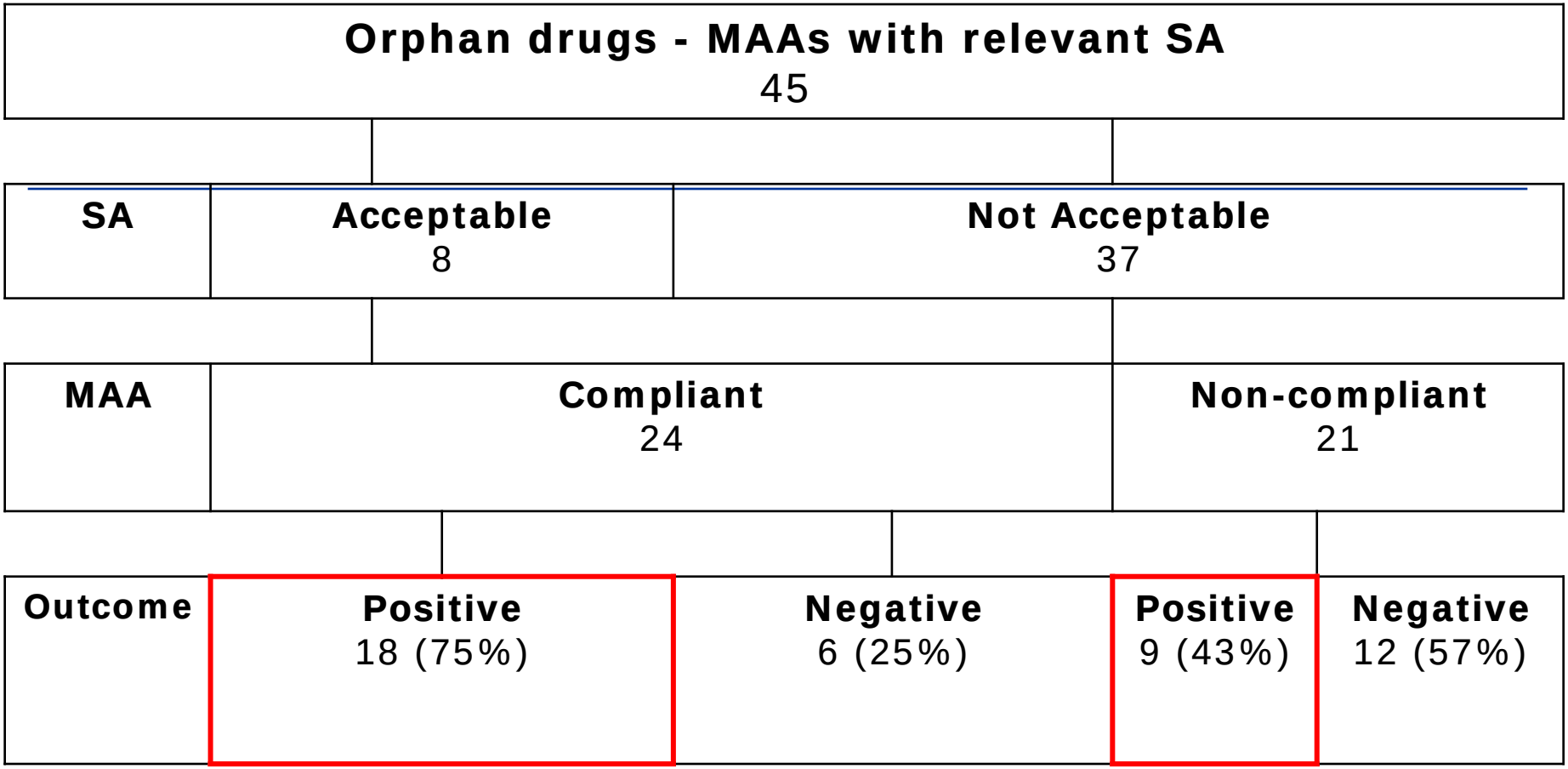
- SAWP meets once a month to discuss quality, non-clinical and clinical questions raised by companies who aim to file for an MAA.
- The process is a 70 day procedure with a first discussion at Day 40 and where there are questions for further clarification an oral explanation with the company at Day 70.
- All responses are endorsed by the CHMP except those regarding Significant Benefit which are endorsed by the COMP.
- The company receives a letter which is not legally binding with the endorsed written responses.

Specifics to the Orphan Medicinal Designation.

- The Orphan Designation legislation states that protocol assistance is an integral part of the services to offer once designation is obtained.
- Orphan Designation is official once the letter is received from the European Commission usually 30days after the COMP recommendation.
- This is a centralised scientific advice through the SAWP. Sponsors can come as often as they want. Fee reductions are applicable depending on status.
- The number of times to seek Scientific Advice should be integrated into development planning in a timely manner to increase efficiencies in project implementation.

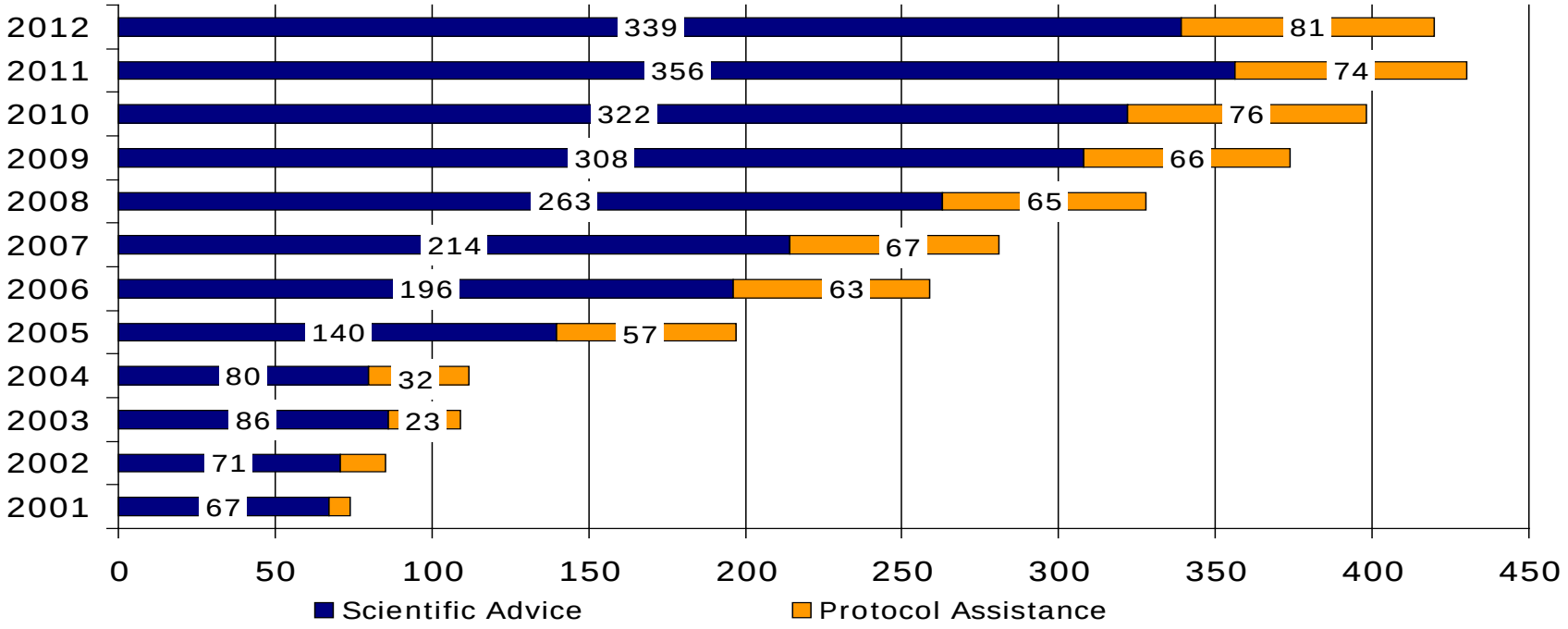
SAWP: Post designation planning

- Companies should integrate this in their development plans and seek advice by coming to pre-submission meetings which are free.
- SAWP pre-submission meetings can be planned in parallel with an orphan designation submission.
- The type of questions need to be discussed with the SAWP Secretariat at the pre-submission before final submission.
- The number of times SAWP advice is needed should be included at crucial development milestones to ensure a greater chance of success. Compliance increases success at time of MAA.

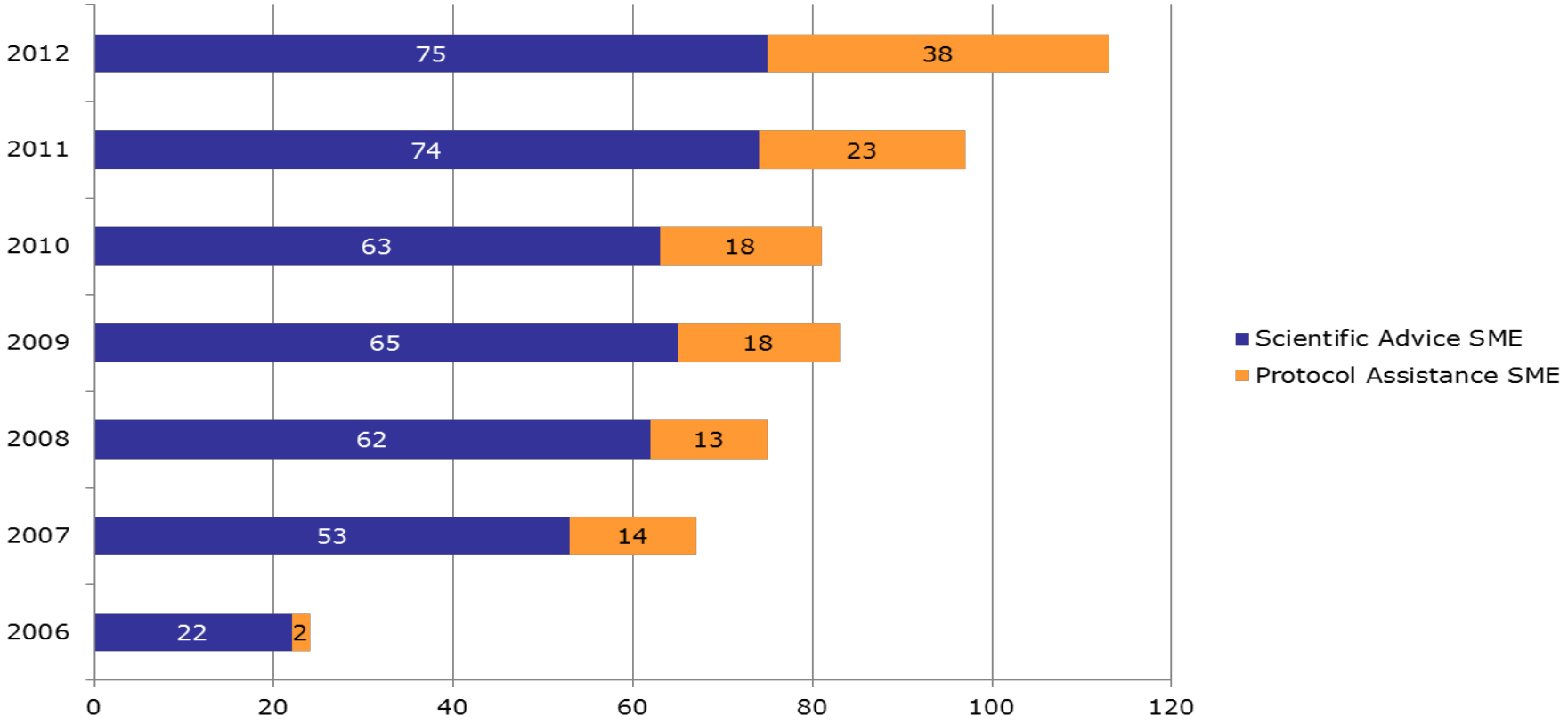


→ Compliance with SA is related to positive outcome

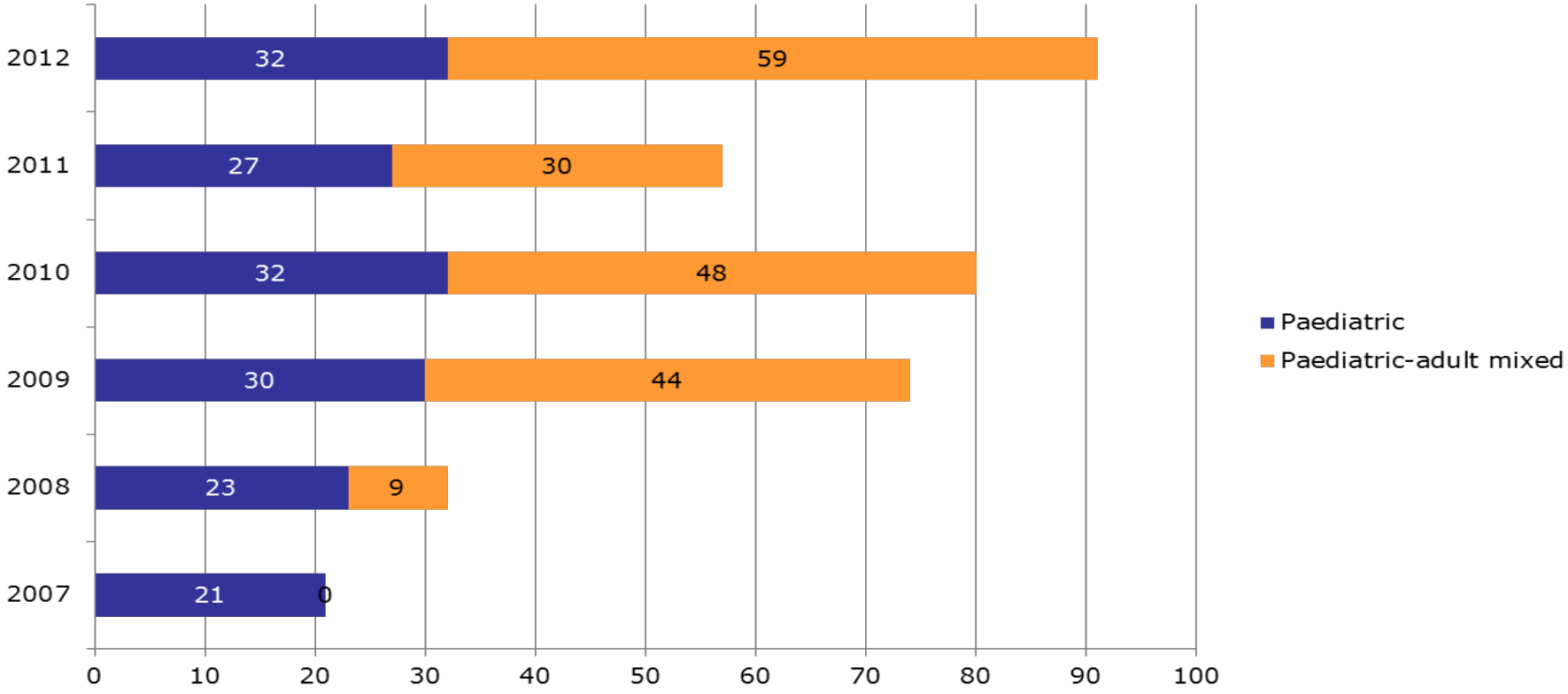
Product related scientific advice and protocol assistance for orphan drugs



Scientific advice main activity so far: product related scientific advice and protocol assistance for SMEs



Scientific advice main activity so far: product related scientific advice and protocol assistance for paediatric and paediatric-adult mixed population



Coordination with Paediatric Needs.

- Difference between EU and US: ODs are not exempted from the obligation to have a paediatric investigation plan or a waiver in the EU before submission of the application for marketing authorisation.
- Sponsors should approach the Paediatric Section at the EMA in a pre-submission meeting to understand what the paediatric development needs of an orphan product will be after Phase I.
- This needs to be built in with other Regulatory consulting activities with the EMA and other Regulatory Agencies.

Paediatric Investigational Plans-PIPs

- If an orphan medicinal product is a new active substance then the sponsor will need to consider a PIP.
- The PIP is obtained from the PDCO which also sits once a month. The PIP needs to be linked to the Orphan Condition.
- A PIP is a 120 day procedure with clock-stops.
- A valid PIP is needed at the time of submission for an MAA and to be eligible for the 2yr extension to the 10yr Market exclusivity.

Conclusions on Development planning.

- After designation and receipt of official letter from the European Commission on Orphan medicinal Designation pre-licencing incentives are available:
- Protocol Assistance through the centralised SAWP which is a 70 day procedure. This is a voluntary fee paying service.
- Paediatric investigation plans which is legally binding in the case of a new active substance. This is a Day 120 procedure.

Annual Report

Dedicated webpage on EMA Website

Annual report on development

Email Print Help Share

This page provides information on the report that sponsors are required to submit to the European Medicines Agency (EMA) every year after their medicine has been granted orphan designation.

These **annual reports on development** provide information on the status of the development of the medicine, including:

- a review of ongoing clinical studies;
- a description of the investigation plan for the coming year;
- any anticipated or current problems in the process, difficulties in testing and potential changes that may have an impact on the medicine's orphan designation.

A **template** for the report is available below, together with a guideline providing advice on the preparation of these reports.

Single report with United States Food and Drug Administration

Sponsors of medicines with orphan designation both in the European Union and the United States (US) can submit a **single report** using the template below to the EMA (via Eudralink) and to the US Food and Drug Administration (FDA) at opdar@fda.hhs.gov.

The submission of a single report to the two agencies is voluntary. The two agencies carry out independent reviews and assessments of the report's contents.

Documents

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Document(s)	Language	Status	First published	Last updated	Effective Date
Annual report on a designated orphan-medicinal-product	(English only)		24/11/2011	03/09/2013	
Note for guidance on the format and content of the annual report on the state of development of an orphan medicinal product	(English only)	adopted	19/02/2009	09/12/2011	

Marketing Authorisation

Marketing authorisation and market exclusivity

If the sponsor of a medicine with an orphan designation submits an application for marketing authorisation to the European Medicines Agency, it should also submit a request for maintenance of the orphan designation in parallel. This enables the Agency to determine whether the medicine can maintain its status as an orphan medicine and benefit from market exclusivity.

Market exclusivity

Medicines that still meet the criteria for orphan designation benefit from the incentive of ten years of **market exclusivity** once they are approved for marketing in the European Union. This protects them from market competition with similar medicines with similar indications once they are approved and is intended to encourage the development of medicines for rare diseases.

Market exclusivity is awarded by the European Commission and is specifically linked to one specific orphan designation for which a marketing authorisation has been granted.

Each orphan designation carries the potential for one market exclusivity for a particular indication. A medicine that has several separate orphan designations for different indications can have several separate market exclusivities if these refer to separate designated conditions.

The period of market exclusivity is extended by two years for medicines that also have complied with an agreed paediatric investigation plan. For more information, see paediatric medicine development.

Evaluation procedure

Market exclusivity is linked to the **maintenance of the orphan designation** when the medicine receives a marketing authorisation for the indication concerned.

The Committee for Orphan Medicinal Products (COMP) reviews the maintenance of orphan designation based on the data available at the time and a report on the maintenance of the designation criteria, which the sponsor supplies at the same time as the application for marketing authorisation. This report includes data on:

- the current prevalence of the condition to be diagnosed, prevented or treated, or the potential return on investment;
- the current life-threatening or debilitating nature of the condition;
- the current existence of other methods for the diagnosis, prevention or treatment of the condition;
- if applicable, a justification of the medicine's significant benefit.

A template for the report is available:

- Sponsor's report on the maintenance of the designation criteria at the time of marketing

Related information

- Orphan designation
- Activities after orphan designation
- Medicines for rare diseases: background information
- Standard operating procedure for review of orphan designation criteria at the time of granting / varying a marketing authorisation (24/05/2012)

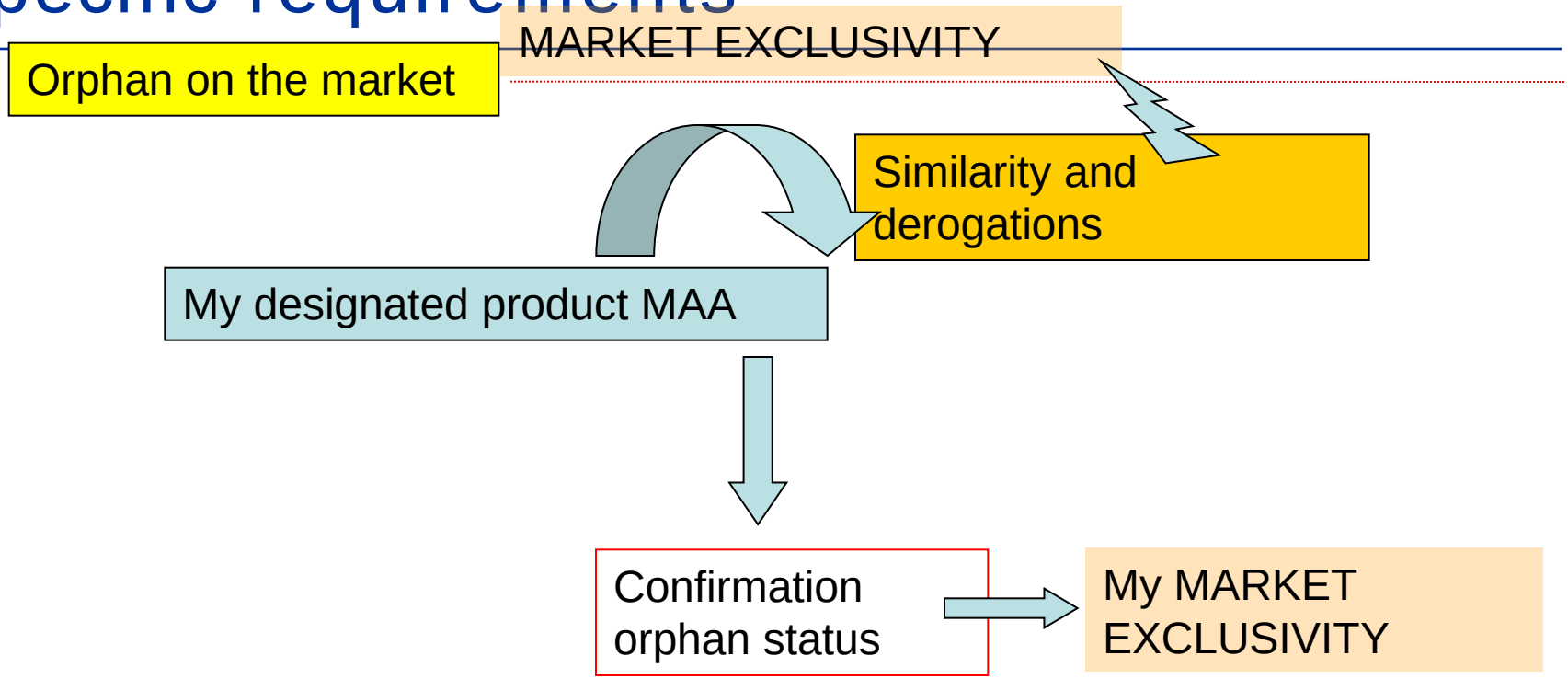
Contact point:

orphandrugs@ema.europa.eu

Authorisation of an orphan drug

- Based on same standards as for non orphan products (quality / safety / efficacy)
- Authorisation only centralised procedure: Regulation 2004/746
- CHMP responsible for assessment
- A valid PIP or waiver at the time of MAA submission.
- Authorisation within designated condition
- More than one designation possible per product (independent incentives)

Specific requirements



Consequence analysis

SIMILARITY

- Non similar: MA assessment goes ahead
- Similar
  - Derogation ok: MA assessment goes ahead
  - No derogation: no possible to grant MA

CONFIRMATION ORPHAN STATUS

- Status confirmed: MA and right to marketing exclusivity
- Status not confirmed: MA but as non orphan (so, no marketing exclusivity)

Specific requirements MAA (I)

Assessment of similarity

- Applies if other orphan medicines authorised for same designated condition
- Need to submit report in module 1.7
  - Molecular structure
  - Mechanism of action
  - Similarity of indication (“significant overlap of populations”?)
- Assessment by CHMP working party competent
- Final opinion by CHMP
- Similarity can be triggered any time before EC decision
- Proactive publication ongoing procedures

Derogations to market exclusivity

Applicable if product is similar

Assessed based on sponsor's report

- Specific timetable (parallel to QSE assessment)

Three derogations (Art 8(2))

- First MAH's consent (agreement market sharing)
- Insufficient supply: long term and clinical consequences (presumably)
- Clinical superiority: better efficacy, better safety or exceptionally major contribution to patient care

Specific requirements MAA (II)

Confirmation designation criteria

- Report to orphan medicines section
  - At time of submission MA
  - Possible to update
- Need to address all designation criteria
- Standard set at time of authorisation
- Assessment by COMP; opinion in parallel with MA opinion by CHMP

Legal basis (I)

Art 5 (12) Regulation (EC) 141/2000

- A designated orphan medicinal product shall be removed from the Community Register of orphan medicinal products:

(...)

(b) if it is established before the marketing authorisation is granted that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned;

(...)

Legal basis (II)

Commission Communication

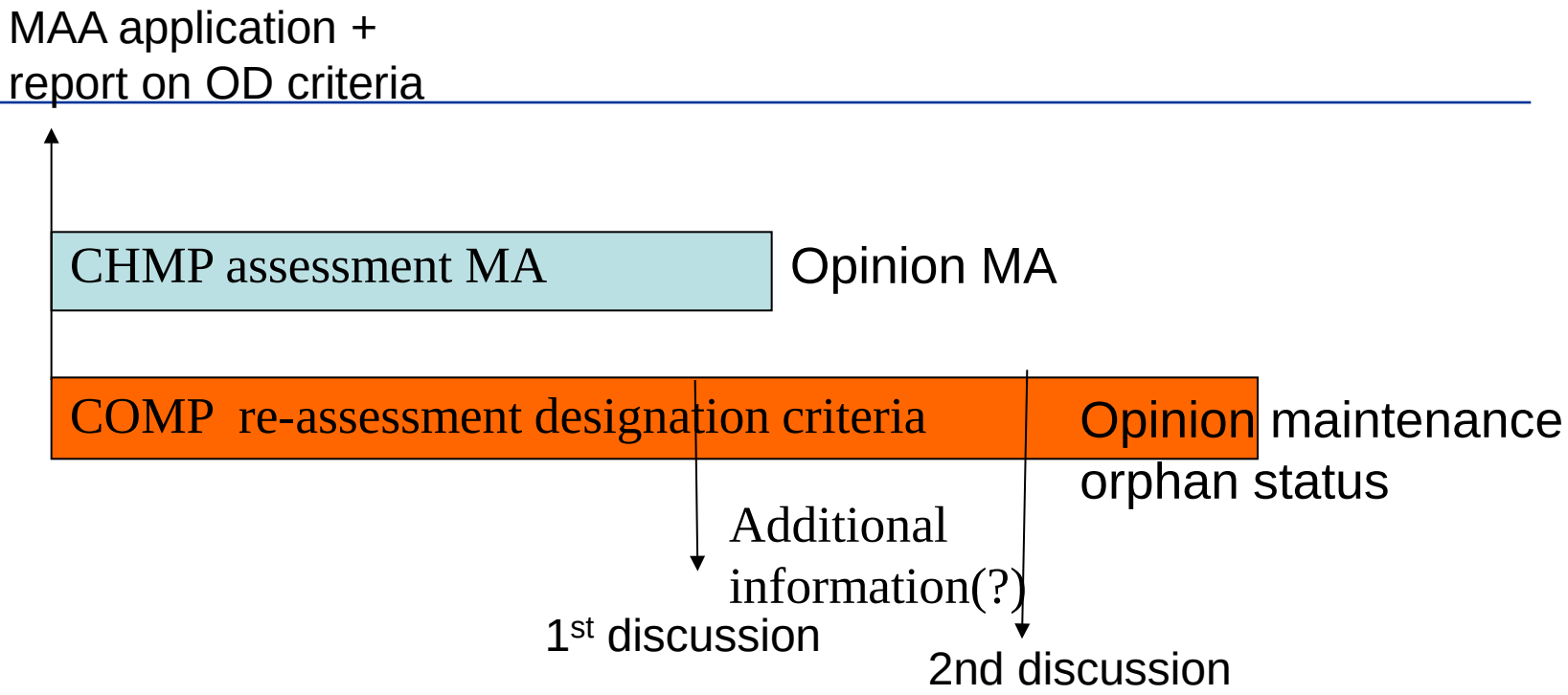
(July 2003; 2003/C 178/02)

- (B.2) removal on basis of Art 5(12)(b) “must be preceded by a re-evaluation by the Committee for Orphan Medicinal Products of the criteria laid down in Article 3”
- “In particular” significant benefit but **not only**
- (B.2.1) report on fulfillment of designation criteria to be sent when Sponsor submits MAA
- Information to be assessed in parallel to the marketing authorisation assessment
- Sponsor may be invited to provide additional information in case of reasonable doubt

Procedure

- Sponsor submits report at the same time submission marketing authorisation application
- Procedure allows two discussions at COMP
- COMP adopts opinion only after CHMP has adopted opinion on marketing authorisation
- Possibility to invite sponsor for oral explanation
- COMP opinion can be subject to appeal
- Final COMP opinion is sent to Commission

·····Opinion


MAA application +
report on OD criteria
CHMP assessment MA
Opinion MA
COMP re-assessment designation criteria
Opinion maintenance orphan status
Additional information(?)
1st discussion
2nd discussion

Requirements

Confirmation prevalence is not more than 5 in 10,000 or insufficient return on investment stands

Confirmation seriousness

Review authorised methods

- If significant benefit applies
  - Exercise of comparison
  - Demonstration assumptions are correct
  - New argument put forward

More on significant benefit

- 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 accompained by data on benefit
- Safety profile is usually characterised after the product is placed on the market

Relevant information available

- Proactive publication of products that start marketing authorisation procedure (COMP and CHMP monthly reports)
- summary of COMP position on the review on web
- Includes information on
  - prevalence
  - seriousness
  - and significant benefit if applicable

- Link to EPAR and vice versa


European Medicines Agency - Human medicines - EU/3/10/752 - Windows Internet Explorer
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2010/09/human_orphan_000802.jsp&mid=WC0b01ac058001d12b
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Orphan designation
Key facts
Review of designation
On 6 June 2010, orphan designation (EU/3/10/752) was granted by the European Commission to Shire Pharmaceuticals Ireland Limited, Ireland, for velaglucerase alfa for the treatment of Gaucher disease.
Expand all items in this list
What is Gaucher disease?
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/3/10/752: Public summary of positive opinion for Velaglucerase alfa for the treatment of Gaucher disease
(English only)
23/06/2010
18/10/2010
Related information
Vpriv: EPAR
Sponsor's contact details:
Shire Pharmaceuticals Ireland Limited
5 Riverside Walk
Citywest Business Campus
Dublin 24
Ireland
Telephone: +353 1 4297700
Telefax: +353 1 4297701
Patients' organisations:
For contact details of patients' organisations whose activities are targeted at rare diseases see:
Orphanet, a database containing information on rare diseases which includes a directory of patients' organisations registered in Europe.
European Organisation for Rare Diseases (EURORDIS), a non-governmental alliance of patient organisations and individuals
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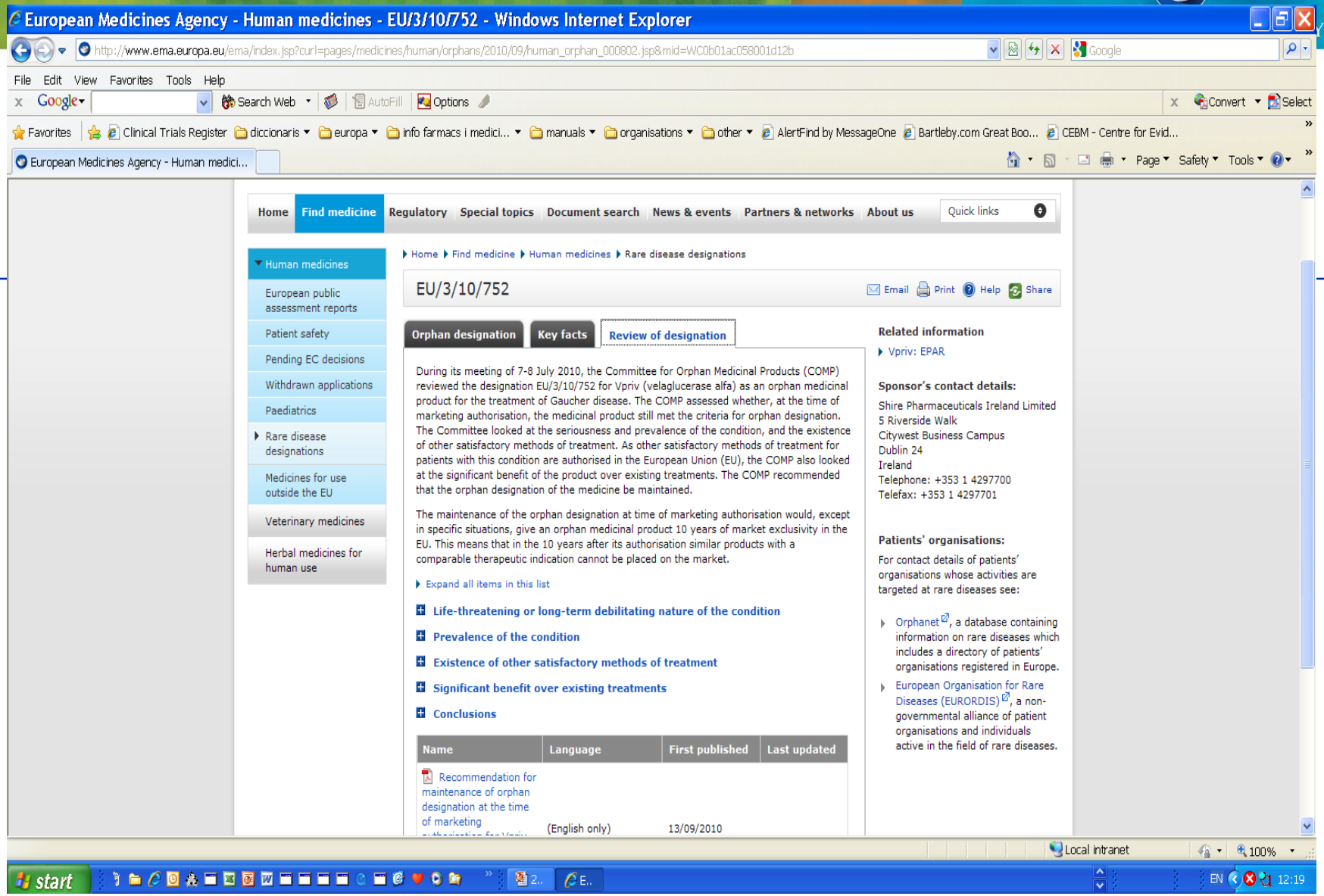
European Medicines Agency - Human medicines - EU/3/10/752 - Windows Internet Explorer
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2010/09/human_orphan_000802.jsp&mid=WC0b01ac058001d12b
File Edit View Favorites Tools Help
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Favorites Clinical Trials Register diccionaris europa info farmacs i medici... manuals organisations other AlertFind by MessageOne Bartleby.com Great Boo... CEBM - Centre for Evid...
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EU/3/10/752
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Orphan designation Key facts Review of designation
During its meeting of 7-8 July 2010, the Committee for Orphan Medicinal Products (COMP) reviewed the designation EU/3/10/752 for Vpriv (velaglucerase alfa) as an orphan medicinal product for the treatment of Gaucher disease. The COMP assessed whether, at the time of marketing authorisation, the medicinal product still met the criteria for orphan designation. The Committee looked at the seriousness and prevalence of the condition, and the existence of other satisfactory methods of treatment. As other satisfactory methods of treatment for patients with this condition are authorised in the European Union (EU), the COMP also looked at the significant benefit of the product over existing treatments. The COMP recommended that the orphan designation of the medicine be maintained.
The maintenance of the orphan designation at time of marketing authorisation would, except in specific situations, give an orphan medicinal product 10 years of market exclusivity in the EU. This means that in the 10 years after its authorisation similar products with a comparable therapeutic indication cannot be placed on the market.
Expand all items in this list
Life-threatening or long-term debilitating nature of the condition
Prevalence of the condition
Existence of other satisfactory methods of treatment
Significant benefit over existing treatments
Conclusions
Name Language First published Last updated
Recommendation for maintenance of orphan designation at the time of marketing
(English only) 13/09/2010
Related information
Vpriv: EPAR
Sponsor's contact details:
Shire Pharmaceuticals Ireland Limited
5 Riverside Walk
Citywest Business Campus
Dublin 24
Ireland
Telephone: +353 1 4297700
Telefax: +353 1 4297701
Patients' organisations:
For contact details of patients' organisations whose activities are targeted at rare diseases see:
Orphanet, a database containing information on rare diseases which includes a directory of patients' organisations registered in Europe.
European Organisation for Rare Diseases (EURORDIS), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.
Local intranet
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Conclusions

- Orphan MA based on same standards as for non orphan products (quality / safety / efficacy)
- Special considerations for market exclusivity other products: similarity and derogations
- Own market exclusivity: confirmation orphan status by COMP
- Authorisation only centralised procedure
- CHMP responsible for assessment
- Authorisation within designated condition
- More than one designation possible per product (independent incentives)