EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Early engagement and support for medicine development

RD-ACTION, European Medicines Agency, and DG SANTE Workshop: How can ERNs add value to clinical research in rare diseases and highly specialised domains?

Presented by Stiina Aarum on 29 May 2018
Human Medicines Research & Development Support Division

General introduction to supportive EMA activities for development of orphan and paediatric medicines:

- Innovation Task Force (ITF)
- Orphan Designation
- Scientific Advice and Protocol Assistance
- Qualification of New Methodologies
- Paediatric Investigation Plan and EnPr-EMA
- PRIME

European regulatory input along drug life cycle

Clinical development

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

MAA

PhV, Reimb.

Paediatric Investigation Plan

Orphan Drug Designation

Scientific Advice/Protocol Assistance

Innovation Task Force

Innovation Task Force (ITF)

Multidisciplinary platform

for **preparatory dialogue and orientation on**

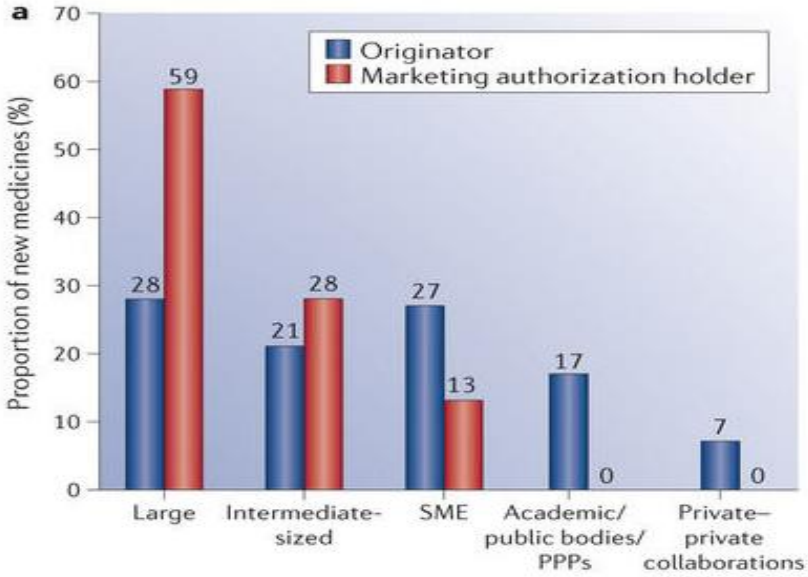
innovative methods, technologies and medicines

ITF objectives

- **Support drug development** via early dialogue on
  - **Scientific, legal and regulatory** issues
  - Products, **methodologies and technologies**
- **Preparing for formal procedures**
- **Address the impact of emerging therapies and technologies** on current regulatory system
- **Assist Knowledge exchange** on innovative strategies involving **regulatory network**

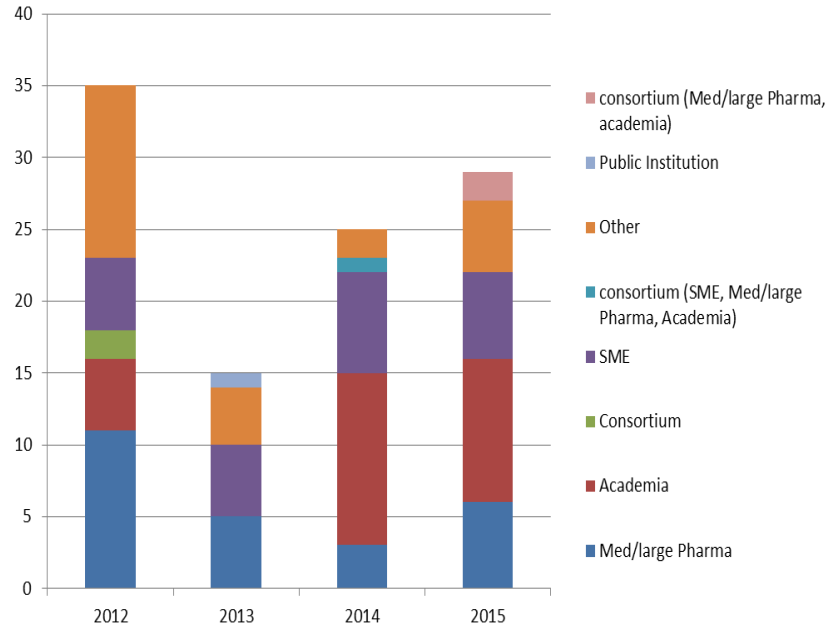
Users of the Innovation Task Force

Originator and the marketing authorization holder for 94 approved products evaluated, divided according to organization type



Regulatory watch: Where do new medicines originate from in the EU? Nature Reviews Drug Discovery Volume: 13, Pages: 92–93; Published online 31 January 2014

S Aarum-Early engagement and support for medicine development



ITF users 2012-2015

Reasons for ITF meetings

92 ITF Briefing meetings organised between 2014 – 2016, of which **80%** were submitted by **academia, SMEs and consortia**

- 15% are Advanced Therapies (Gene, Cell, Tissue engineered products)
- 14% consider seeking EU Orphan Drug designation (rare diseases)
- 20% consider interaction with the EMA Paediatric Committee (PDCO)
- 30% of applicants consider applying a formal scientific advice request
- 11% consider Qualification of methodology (e.g. Biomarker qualification)
- 10% consider Marketing Authorisation Application within foreseeable future

Orphan designation

Main characteristics:

- For medicinal products for human use
- Procedure free of charge; request at any stage of development
- Sponsor can be either company or individual
  - Established in the Community (EU, Ice, Liech, Nor)
- COMP assessment, max. 90 days procedure
- European Commission Decision gives access to incentives

Reg (EC) No 141/2000 of the European Parliament and of the Council Products of 16 December 1999

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

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 SMEs

- 10-year market exclusivity (+ 2 if paediatric)

  - Protection against similar products

  Product development

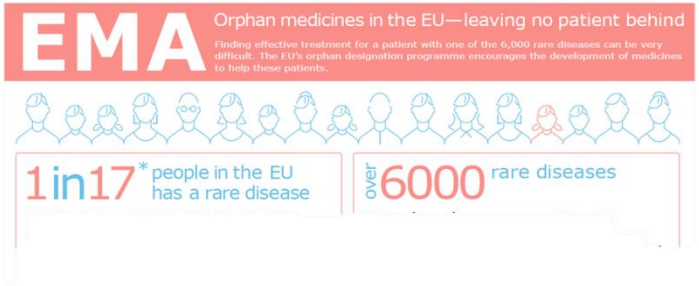
  - Protocol assistance, reduced fee

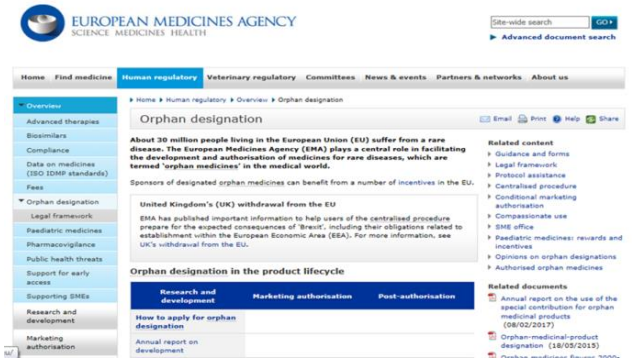
- Community marketing authorisation

- National incentives (EC inventory)

Achievements of the EU Orphan Regulation

- Stimulated sponsors to develop medicinal products for rare diseases
- From 2000 to 2017, 1,952 orphan designations have been issued by the European Commission, of which 142 have resulted in authorised medicinal products
- The orphan designations cover a wide variety of rare diseases, including genetic diseases and rare cancers, for which there are limited treatment options, a large number of these diseases also affect children





S Aarum-Early engagement and support for medicine development

Scientific Advice and Protocol Assistance

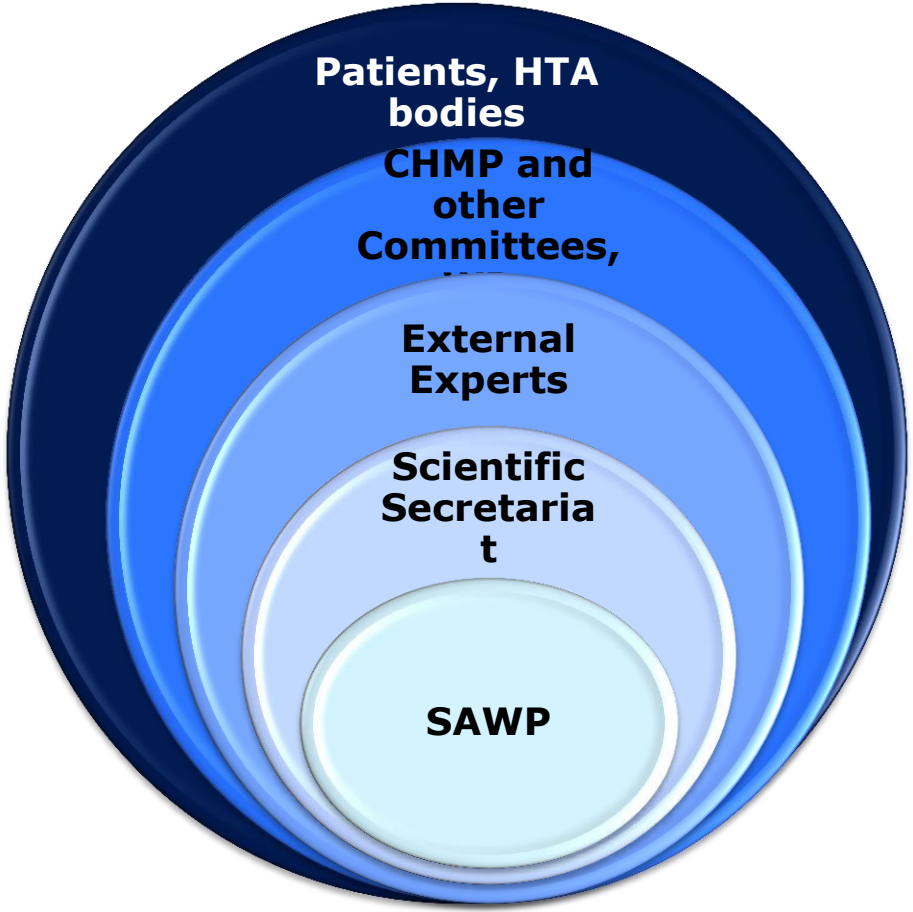
Advising developers on specific questions they have during development of medicines to meet regulatory and scientific requirements:

- how to manufacture them;
- how to test them in different models; and
- how to test them in humans in clinical trials.
- how to study them in specific populations e.g. rare diseases and children
- prospective in nature

Article 57-1 (n) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004

Scientific Advice Working Party

- Working Party of the Committee for Human Medicinal Products (CHMP)
- 30 experts from national authorities, universities and hospitals chosen by required expertise
- Monthly four day meetings in EMA
- Scientific and logistic support from EMA staff
- Networking with EU experts
- Key platform for collaboration with health technology assessment (HTA) bodies

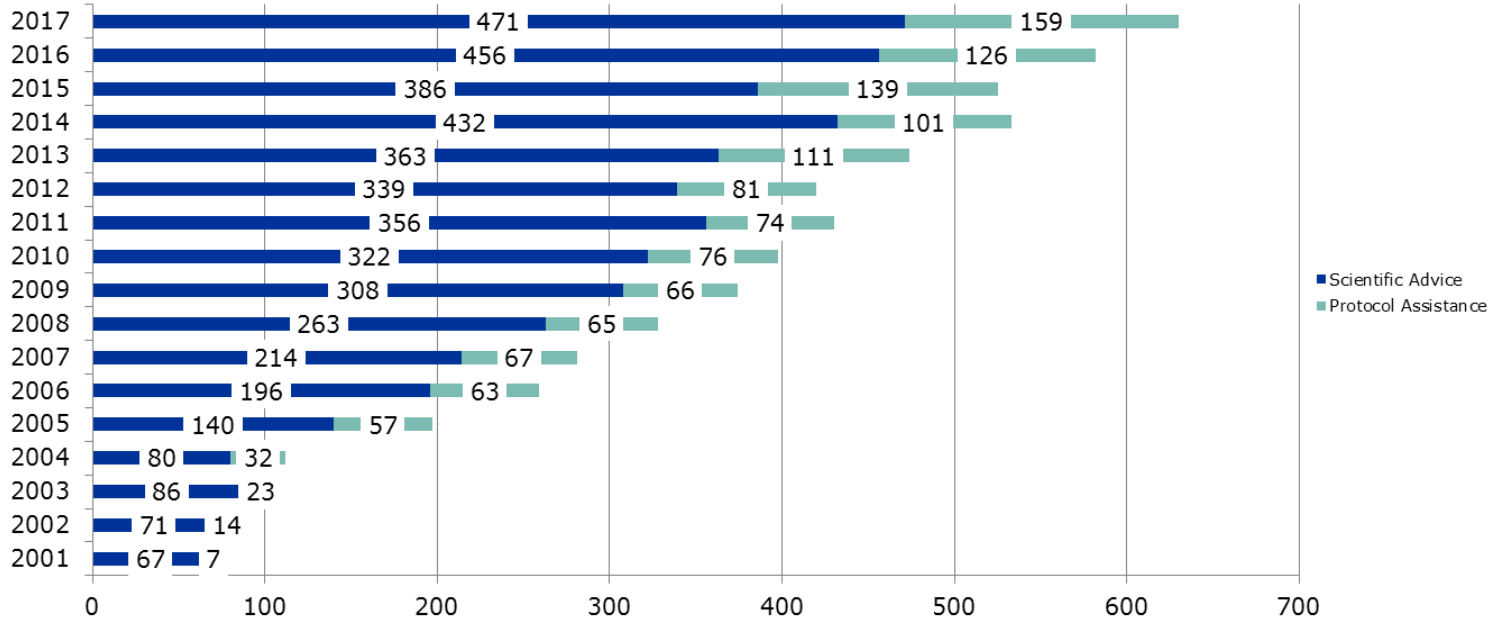


Scientific advice / Protocol Assistance

Voluntary, not mandatory procedure:

- Developers ask questions;
- Responses are prepared and discussed;
- In 50% of the cases, in particular when the experts do not agree with the developer's proposal, a face-to-face meeting with the developer is organised;
- Written responses are adopted by the CHMP and send to the developer (Final Scientific advice letter);
- Short procedure: 40 days or 70 days when a face-to-face meeting takes place.
- Fee reductions
- Obtaining and complying with SA is strongly associated with a positive MAA outcome (Hofer et al. 2015; 2018)

Scientific Advice main activity so far: scientific advice and protocol assistance



Qualification of novel methodologies and biomarkers

Procedure to guide the development of new more efficient ways to develop drugs, e.g. development of new endpoints for clinical trials

Vision:

- speed up/optimise drug development and utilisation
- improve public health

Qualification

- …on the regulatory validity and acceptability of a specific use of a proposed method in R&D context (in non-clinical and clinical studies)
- **Voluntary**, scientific pathway for innovative methods or drug development tools not yet integrated in the drug development and clinical management paradigm

One procedure with **two outcomes**:

- Qualification Advice, OR
- Qualification Opinion

Who can apply? Consortia, Networks, Public / Private partnerships, Learned societies, Pharmaceutical industry.


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Qualification advice

- On future protocols and methods for further method development towards qualification
- The advice is based on the evaluation of the scientific rationale and on the preliminary data submitted to the Agency
- The procedural route is not fixed but will follow the assessment of the data

Letter of support

- Based on qualification advice, when the novel methodology under evaluation cannot yet be qualified but is shown to be promising based on preliminary data.
- Aim to encourage data-sharing and to facilitate studies aimed at eventual qualification for the novel methodology under evaluation.
- A high-level summary of the novel methodology, context of use, available data, and on-going and future investigations. The Agency publishes letters of support, if the sponsor agrees.

Letter of support for Patient Data Platform for capturing patient-reported outcome measures for Dravet syndrome

On 09 December 2015 the applicant Dravet Syndrome Foundation Spain requested qualification opinion for Patient Data Platform as an electronic tool for capturing patient reported outcomes in paediatric epilepsies, pursuant to article 57(1)(n) of regulation (EC) 726/2004 of the European Parliament and of the Council.

Qualification opinion

- Publicly available
- on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data

Qualification opinion - The European Cystic Fibrosis Society Patient Registry (ECFSPR)

Back to top

Document(s)	Language	Status	First published	Last updated	Effective Date
Qualification opinion - The European Cystic Fibrosis Society Patient Registry (ECFSPR)	(English only)	draft: consultation open	09/02/2018		

Examples of Novel Methodologies

- Biomarkers
- Clinical Outcome Assessments (PRO, ClinRO, ObsRO)
- Imaging Markers
- Symptom Scales
- Animal Models
- Statistical Methods

122 procedures since start in 2008

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 December 2017
EMA/750178/2017

Essential considerations for successful qualification of novel methodologies

Modelling and simulation

Early contribution before MAA: Enable early informed discussion with sponsors regarding study designs, endpoints, dose regimens, paediatric questions, data needed to support benefit risk decisions

At MAA:

- Support benefit risk decisions by investigating uncertainties & untested scenarios, and their clinical consequences
- Translate benefit risk from the population to individual
- Inform (SmPC) for special populations

Post Marketing: Lifecycle management of products

Objectives of the EU Paediatric Regulation

Improve the health of children:

- Increase high quality, ethical **research** into medicines for children
- Increase **availability** of authorised medicines for children
- Increase **information** on medicines

Achieve the above:

- Without unnecessary studies in children

Main pillars:

- Committee for Paediatric Medicines (PDCO)
- Paediatric Investigation Plan (PIP)
- Procedures
- Incentives; reward to completed PIPs

Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006

Paediatric Investigation Plan (PIP)

- Basis for development and authorisation of a medicinal product for all paediatric population subsets.
- Includes details of the timing and the measures proposed, to demonstrate:
  - Quality
  - Safety
  - Efficacy

  } Marketing Authorisation Criteria
- To be agreed upon and/or amended by the PDCO
- Binding on developer → compliance check
  (but modifications possible, at the developer's request)

When is a PIP/Waiver necessary and when to request?

- New marketing authorisation
- Already authorised product:
  - New indications
  - New routes of administration
  - New formulations (but not for new strengths)
- **Timing:** not later than upon completion of the human pharmaco-kinetic studies in adults. PIP amendments during the development; compliance check at the time of MAA.

Achievements of the EU Paediatric Regulation

Positive impact on paediatric drug development:

- More medicines for children-new medicines for use in children and new pharmaceutical forms appropriate for children were authorised in the EU;
- Better and more information for prescribers and patients -updates of the product information;
- Better paediatric research and development;
- More regulatory support for paediatric matters;
- Paediatrics now being an integral part of medicine development.

* https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/2017_childrensmedicines_report_en.pdf

European Network of Paediatric Research at the European Medicines Agency (**Enpr-EMA**)

- Umbrella network of existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population *(Art 44 Paediatric Regulation)*
- Set up to facilitate studies relating to paediatric medicinal products
- Enables collaboration/learning of individual networks from each other
- Minimum recognition criteria to become a member
- Enpr-EMA members perform research with children in multiple therapeutic areas and different stages of development
- Fully searchable Enpr-EMA database of all listed networks
- Contact: enprema@ema.europa.eu

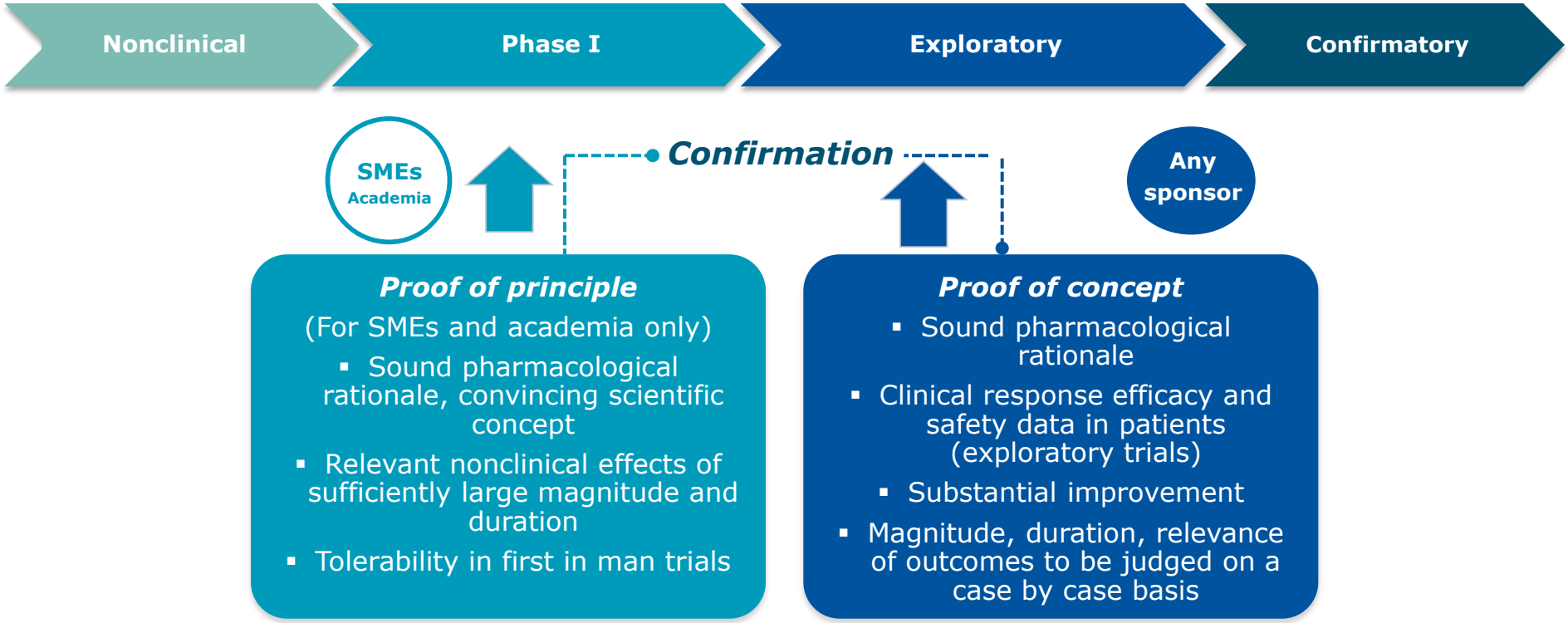
Useful links – Paediatric medicines

PRIority Medicines (PRIME) scheme

- Early access tool targeting medicinal products (not yet authorised) of major public health interest, supporting patient access to innovative medicines.
- New product shows potential to address to a significant extent an unmet medical need.
- No application fee for the 40-d procedure.
- Incentives: potential for accelerated MAA assessment, early CHMP Rapporteur appointment, kick off meeting with multidisciplinary expertise from EU network, enhanced SA, EMA contact point.
- Fee incentives for SMEs and academics on Scientific Advice requests.

Recital 33 and Article 14(9) of Regulation (EC) No 726/2004

Entry points PRIME eligibility and required evidence



S Aarum-Early engagement and support for medicine development

PRIority Medicines (PRIME) scheme

- 177 requests for eligibility to PRIME received since March 2016.
- More than half of the applications from SMEs.
- Requests in a wide range of therapeutic areas, being the majority for oncology or haematology products.
- Of the total 36 medicines included 30 are for rare diseases.
- High number of requests for advanced therapy medicines (40% of products granted eligibility).
- PRIME products have received enhanced support from the Agency: 31 kick-off meetings; 37 scientific advices

Summary-early engagement and support for medicine development

- The EMA is open to discuss scientific, regulatory and technical aspects of innovative developments
- SA/PA is key tool to promote the collection of robust data on the benefits and risks of medicines and to collaborate with HTA bodies
- SA/PA benefits patients as it promotes the generation of robust data and protects them from participating in badly designed or irrelevant clinical trials
- Specific support and fee incentives exist for rare and paediatric diseases
- Regulatory incentive via PRIME is possible for medicinal products of major public health interest and in particular from the viewpoint of therapeutic innovation

Thank you for your attention

Further information

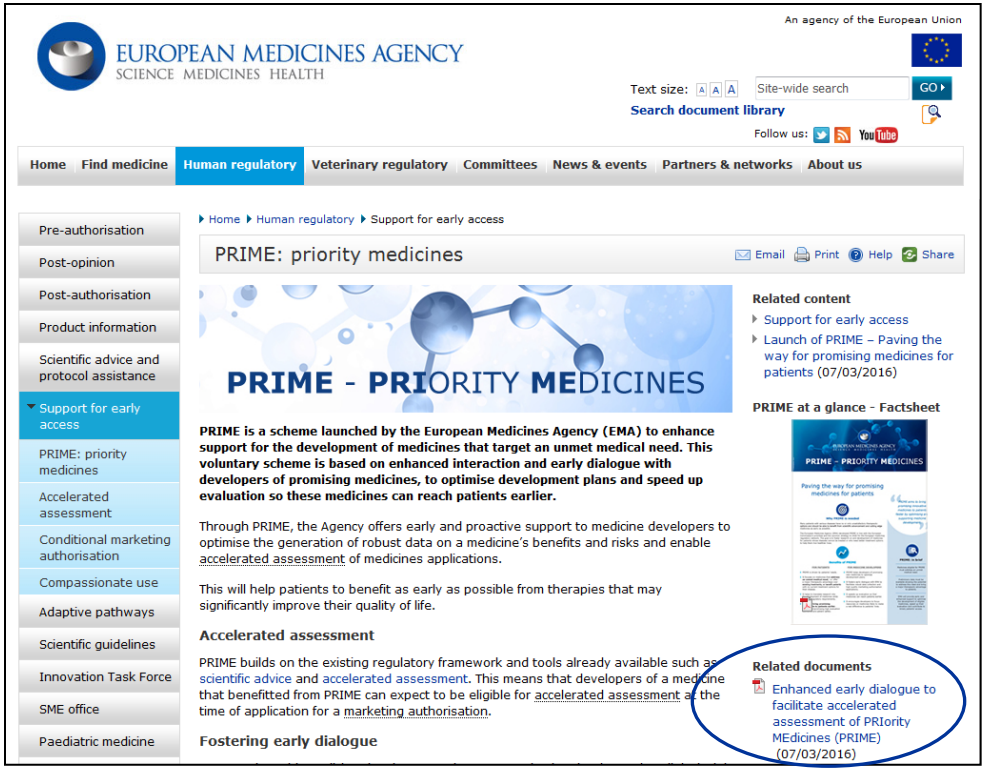
Stiina.aarum@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Follow us on **@EMA_News**

Back-up slides

PRIME webpage and supporting documents



Factsheet in lay language

Q&A, templates, application form for applicants

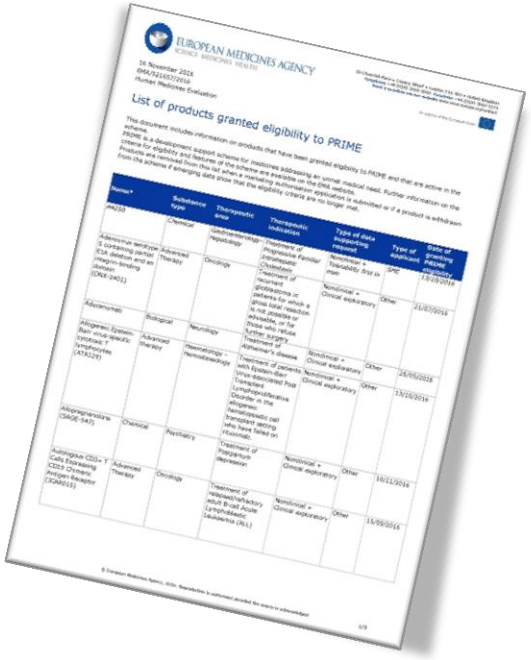
prime@ema.europa.eu

Transparency

Publication of monthly reports

- Broad characteristics
- Active substance (for eligible products only)
- High-level statistics

List of products granted eligibility to PRIME



Procedures evaluated by the PDCO

- PIP application: 120-day procedure, clock-stop at D60 (Request for Modification)

Deferrals for initiation and/or completion of some measures are possible

- PIP modification: 60-day procedure, no clock-stop

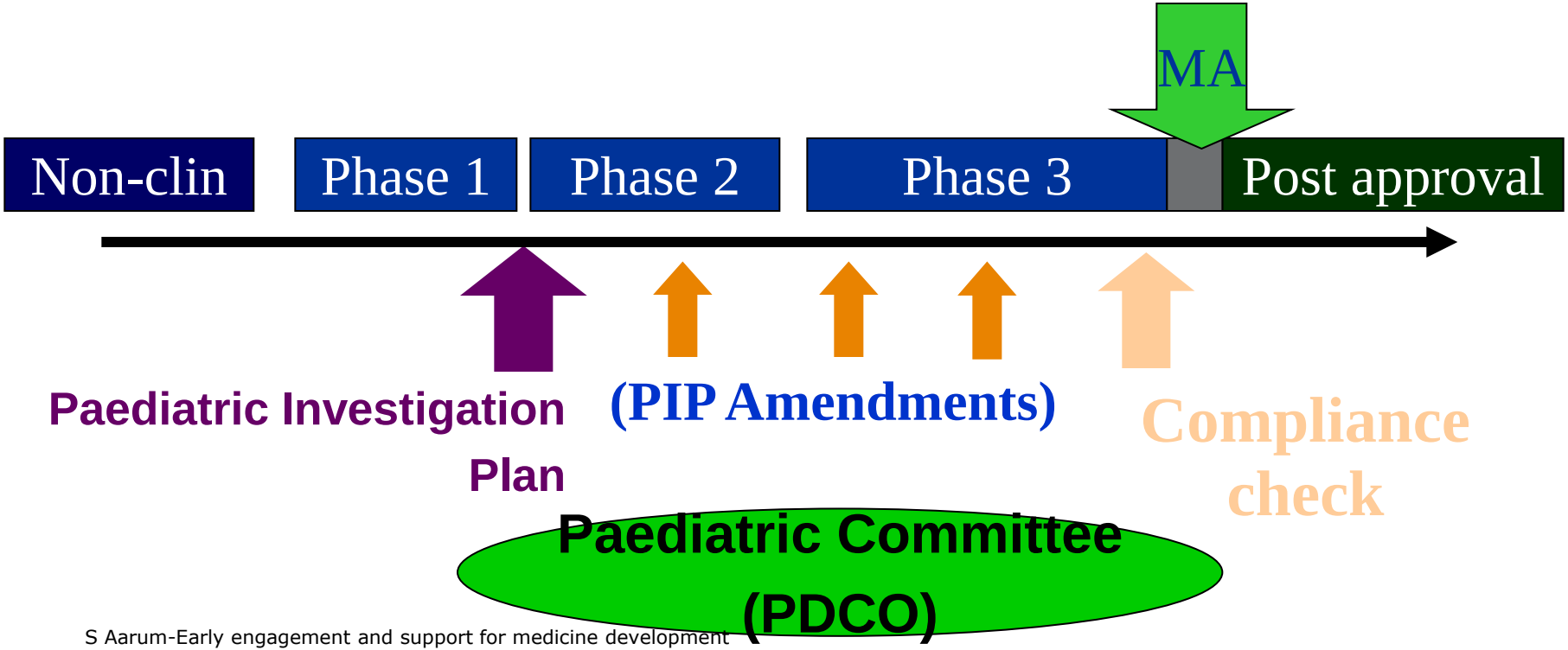
  ⟶ PDCO Opinion, EMA Decision (partially published on EMA website)

- PIP Compliance check: 60-day procedure, no clock-stop

  ⟶ PDCO Opinion (outcome published on EMA website)

- Confirmation of class waiver
- Inclusion of an indication within an agreed condition

When should the PIP be requested?



Answers to Questions received

EUROPEAN MEDICINES AGENCY

Q: Will network representatives be involved in the committees' assessment to bring their expertise to conclude to the best way forward for the PIP

An agency of the European Union

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Text size: A A A | Site-wide search | GO | Search document library | Follow us: YouTube

Home | Find medicine | Human regulatory | Veterinary regulatory | Committees | News & events | Partners & networks | About us

Pre-authorisation
Post-opinion
Post-authorisation
What we publish
Product information

Home ▸ Human regulatory ▸ Paediatric medicine ▸ Research and development ▸ Paediatric investigation plans
PIPs: Questions and answers

Paediatric investigation plans: questions and answers

Email | Print | Help | Share

This page provides detailed guidance for companies intending to apply for a paediatric investigation plan (PIP), waiver or deferral, as well as for companies that already have an agreed PIP. The information is available as questions and answers, which the European Medicines Agency (EMA) revises as necessary.

European Network for Paediatric Research at the European Medicines Agency (Enpr-EMA)

Back to top

Collapse all items in this list

Why should I consider involving paediatric networks when preparing the PIP?

Early involvement of clinical research networks may help to develop a PIP in a number of ways, and should be considered when preparing the application, as recommended in the EU Guideline on the Format and content of PIP and waiver applications.

Enpr-EMA, which is coordinated by the Agency, provides a contact point for a number of specialty and multi-specialty networks. Areas of expertise that can be offered by Enpr-EMA members are reported in the Enpr-EMA database.

Networks may provide assistance in the following areas:

- identification of existing databases;
- location of study sites and investigators to conduct natural history studies;
- access to clinicians who can provide data about patient throughput or develop bespoke feasibility assessments;
- definition of important paediatric needs, priorities and relevant outcomes;
- identification of acceptable trial procedures / visit schedules;
- clarification of other scientific questions.