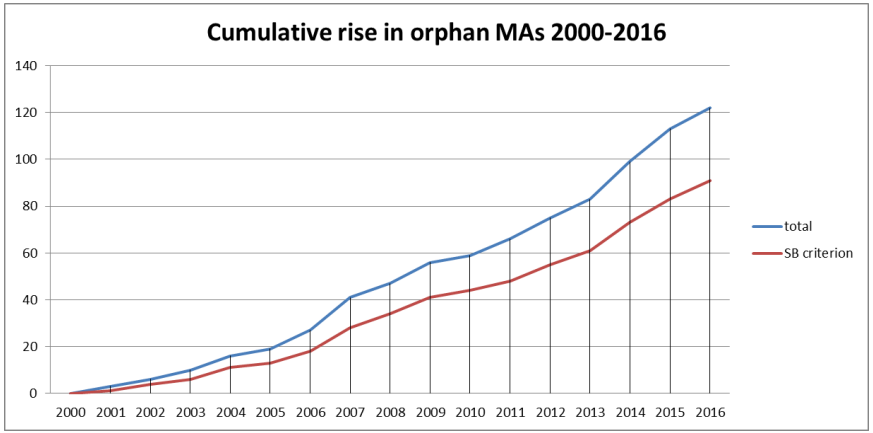
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Supporting orphan medicines development and addressing significant benefit requirements through protocol assistance

SME Info Day

Presented by Matthias Hofer on 17 November 2017
Scientific Officer, Orphan Medicines Office

Orphan environment after 16 years of EU orphan legislation



- Success of EU orphan legislation
- 128 orphan MAs until 2016 and rising
- ~ 75% require demonstration of SB
- Crowded areas, e.g. oncology, haematology, pulmonology

SMEs* develop a large proportion of orphan medicinal products

TABLE 1

Differences in characteristics between orphan and non-orphan medicines marketing authorisations[a]

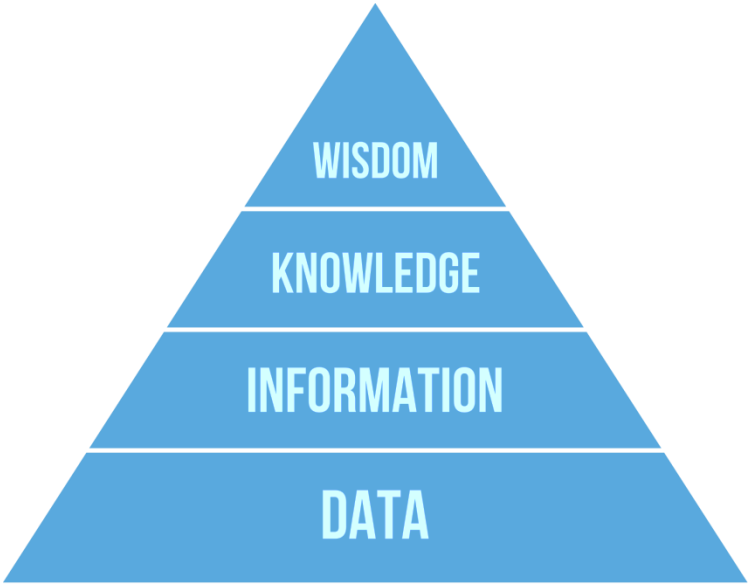
Independent variables	Non-orphan (n=475)	Orphan (n=157	Non vs Orphan	All MAA
MAA outcome				
Negative	101 (21%)	53 (34%)	$P = 0.0017$	154 (24%)
Positive	374 (79%)	104 (66%)		478 (76%)
Exceptional circumstances				
No	457 (96%)	127 (81%)	$P < 0.001$	584 (92%)
Yes	18 (4%)	30 (19%)		48 (8%)
Conditional approval				
No	461 (97%)	139 (89%)	$P < 0.0001$	600 (95%)
Yes	14 (3%)	18 (11%)		32 (5%)
Product type				
Biologic	159 (33%)	37 (24%)	$P = 0.0058$	196 (31%)
Known substance	95 (20%)	49 (31%)		144 (23%)
New chemical entity (NCE)	221 (47%)	71 (45%)		292 (46%)
Therapeutic area				
Endocrine and metabolic disorders	61 (13%)	12 (8%)	$P < 0.0001$	73 (12%)
Infectious diseases	100 (21%)	9 (6%)		109 (17%)
Neurologic and psychiatric disorders	65 (14%)	9 (6%)		74 (12%)
Oncology	56 (12%)	62 (39%)		118 (19%)
Other	193 (41%)	65 (41%)		230 (36%)
Company size				
Large	234 (49%)	43 (27%)	$P < 0.0001$	277 (44%)
Medium	129 (27%)	38 (24%)		167 (26%)
Small	112 (24%)	76 (48%)		188 (30%)

* small, medium and large enterprises were categorised based on Scrips rankings

Study duration 2000-2013

Hofer MP et al, Drug Discov Today. 2017 Oct 23

Outline



- Protocol assistance with SB answer
- EMA support on orphan criteria
- Incentives
- Orphan legislation & EC Notice 2016

Legal background

1. Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products of 16 December 1999
   - COMP
   - Criteria for designation,
   - Incentives and procedure

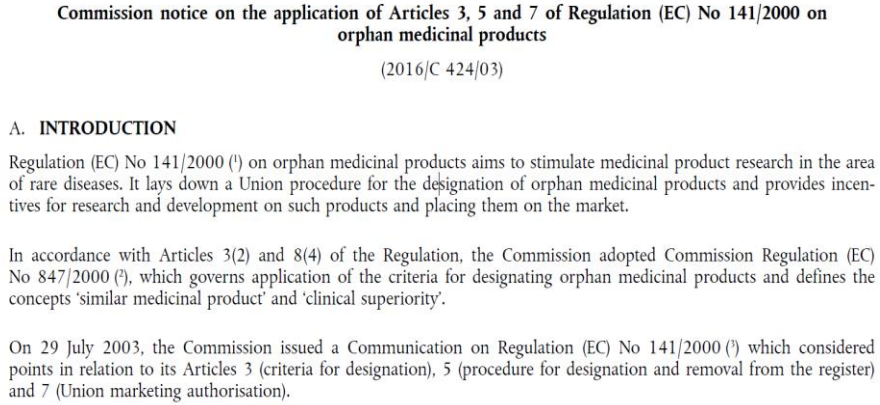
2. Commission Regulation (EC) No 847/2000 of 27 April 2000

3. 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)

Criteria for EMA orphan designation

1. Product intended for diagnosis, prevention or treatment
2. Serious condition (life threatening or chronically debilitating)
3. Affecting not more than 5 in 10,000 **or** insufficient return on investment
4. No satisfactory treatments **or** significant benefit over satisfactory methods ( )

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



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)

A. **INTRODUCTION**

Regulation (EC) No 141/2000 (1) on orphan medicinal products aims to stimulate medicinal product research in the area of rare diseases. It lays down a Union procedure for the designation of orphan medicinal products and provides incentives for research and development on such products and placing them on the market.

In accordance with Articles 3(2) and 8(4) of the Regulation, the Commission adopted Commission Regulation (EC) No 847/2000 (2), which governs application of the criteria for designating orphan medicinal products and defines the concepts 'similar medicinal product' and 'clinical superiority'.

On 29 July 2003, the Commission issued a Communication on Regulation (EC) No 141/2000 (3) which considered points in relation to its Articles 3 (criteria for designation), 5 (procedure for designation and removal from the register) and 7 (Union marketing authorisation).

- Prevalence can equal 0
- Re-assessment of orphan criteria at time of variation may be requested
- Significant benefit discussion versus hospital preparations (magistral/officinal) of the same active substance

EMA and EU incentives

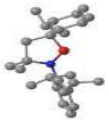
Pre marketing authorisation

- Fee reductions for regulatory procedures, extended for SMEs
- Access to centralised EU wide marketing authorisation
- Access to national and EU incentive programs (Horizon 2020)

Post marketing authorisation

- 10 (+2) year market exclusivity: protection against similar products
- Fee reductions for regulatory procedures

European regulatory input along drug life cycle



Clinical development

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

ATMP Certification & Classification procedures

Scientific Advice/Protocol Assistance

Orphan Drug Designation | **Review** | **Variation**

Paediatric Investigational Plan

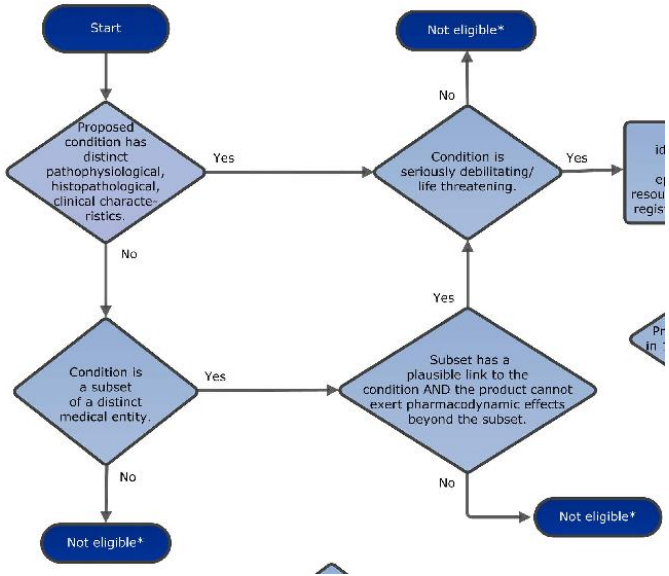
MAA

PhV & PSE

EMA support for orphan designation and maintenance

- ✓ EMA orphan designation website
- ✓ Pre-submission meetings (designation) and pre-validation meetings (review) NEW
- ✓ COMP minutes (monthly on EMA website)
- ✓ OMAR – **O**rphan **M**aintenance **A**ssessment **R**eport (published with EPAR) NEW
- ✓ Scientific publications NEW
- ✓ Orphan designation queries via orphandrugs@ema.europa.eu / AskEMA system
- ✓ Protocol assistance queries via scientificadvice@ema.europa.eu / AskEMA system

Orphan condition



Tsigkos *et al. Orphanet Journal of Rare Diseases* 2014, **9**:13
http://www.ojrd.com/content/9/1/13

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Use of biomarkers in the context of orphan medicines designation in the European Union

Stelios Tsigkos[1*], Jordi Llinares[1], Segundo Mariz[1], Stiina Aarum[1], Laura Fregonese[1], Bozenna Dembowska-Baginska[2], Rembert Elbers[4], Pauline Evers[2], Tatiana Foltanova[3], Andre Lhoir[2], Ana Corrêa-Nunes[2], Daniel O'Connor[2], Albertha Voordouw[5], Kerstin Westermark[2] and Bruno Sepodes[2,6]

Abstract

The use of biomarkers within the procedures of the Committee of Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) is discussed herein. The applications for Orphan Medicinal Product designation in the EU are evaluated at two stages. At the time of orphan designation application, the file undergoes an assessment to establish whether the proposed condition is a distinct and serious condition affecting not more than 5 in 10,000 people in the EU, and whether the product is plausible as a therapy for that condition. In cases where therapies already exist, the

Medical plausibility

- Nonclinical or preliminary clinical data
- Relevant models
- Data with the proposed product
- Relevant outcomes

Prevalence

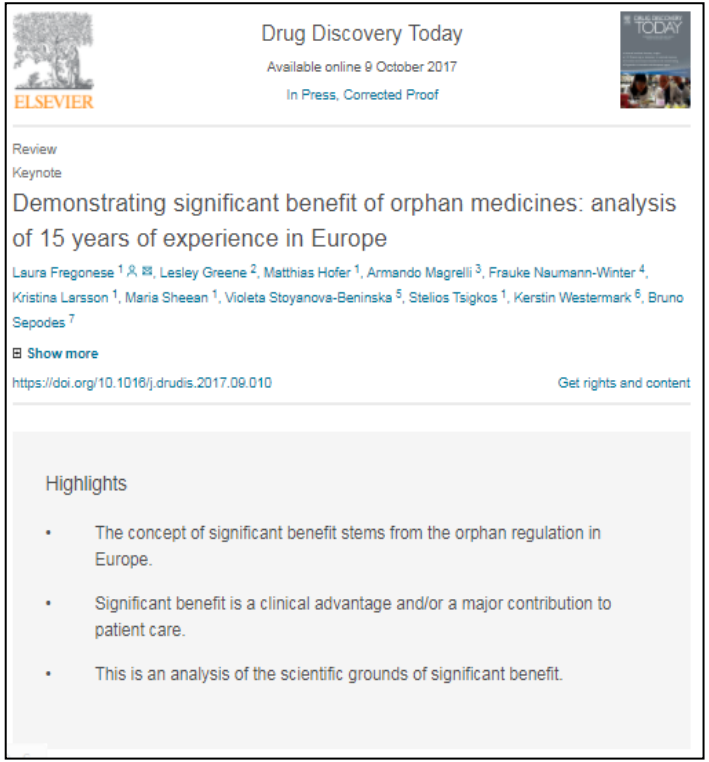
- Clear case definition and consideration of duration
- Treatment indications: full point prevalence unless duration <12m
- Diagnosis and Prevention: annual number of eligible population

Significant benefit I

- DATA to support a comparative discussion

- Discuss your orphan product vis a vis the satisfactory products to show improved effects, add-on effects, targeting different aspects or populations, major contribution to patient care

NEW



ELSEVIER

Drug Discovery Today

Available online 9 October 2017

In Press, Corrected Proof

Review

Keynote

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], Bruno Sepodes [7]

Show more

https://doi.org/10.1016/j.drudis.2017.09.010

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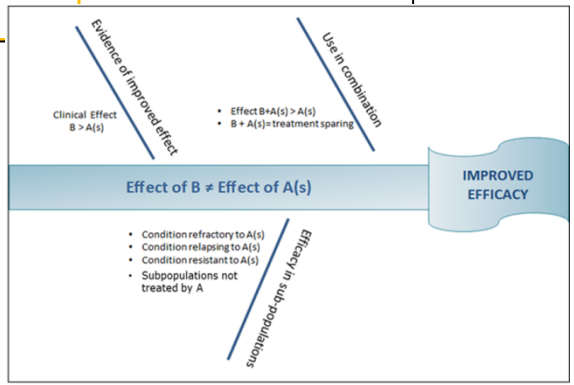
Highlights

- The concept of significant benefit stems from the orphan regulation in Europe.
- Significant benefit is a clinical advantage and/or a major contribution to patient care.
- This is an analysis of the scientific grounds of significant benefit.

Significant benefit II

Clinically Relevant Advantage

Improved Efficacy	Improved Safety
Use in Combination	Less serious ADRs Less severe ADRs Less frequent ADRs
Efficacy in Sub-populations	Treatment-sparing
Better Clinical Effect	



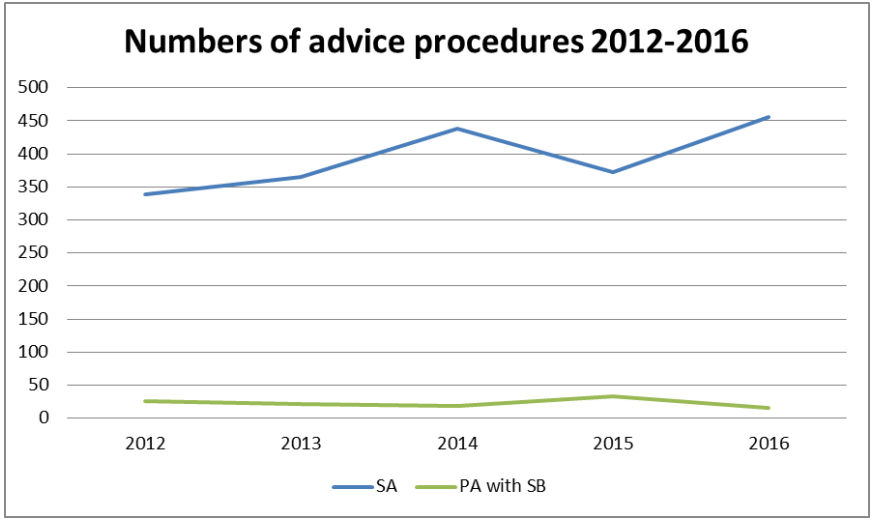
Major Contribution to Patient Care

Ease of use	Availability*
Formulation/ administration route	Shortage of supply
Dosing schedule	Centralized MA
Compliance	
Other	

Fregonese et al, Drug Discov Today. 2017 Oct 9

Maintenance of orphan designation with significant benefit

- Observations on orphan MAAs in 2016
  - Products that received previous PA+SB kept orphan status
  - More important role for PA+SB
- The number of PA+ SB not rising



COMP priority is to foster early dialogue on SB via EMA PA procedure

Kind invitation for SME sponsors to use the tool of PA+SB

COMP raises their hands for Rare Disease Day 2017

When should SB question be asked?

Clinical development

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

Orphan Drug Designation | **Review** | **Variation**

SA | **PA** | **PA+SB (initial and subsequent variations)**

Iterative PA

- Cumulative body of evidence over time
- Updates to clinical development
- Changes in regulatory environment, e.g. EC notice 2016/C 424/03
- Changes in authorised competitors

- PA with SME fee reductions allow for iterative PA process
- SB question has to be part of PA procedure with other questions
- Combination with other initiatives, e.g. PRIME, HTA parallel advice

Significant benefit question

Does the COMP agree with the proposed strategy to demonstrate significant benefit of *xyz* over currently authorised products?

- ✓ Link to clinical development plan discussed with SAWP/CHMP -> endpoints, comparators
- ✓ "clinically relevant advantage" or "major contribution to patient care"
- ✓ Target population/proposed therapeutic indication -> best standard of care outlining authorised products of relevance
- ✓ Planned methodology (direct/indirect/bibliographical etc)
- ✓ Major contribution to patient care: specify and discuss patient-centric measurements
- ✓ Mechanism of action/ nonclinical evidence/improved PK profile/ "self-evidence"

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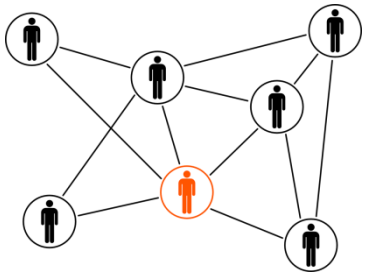
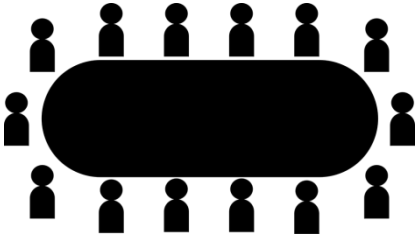
Who provides COMP SB answer?

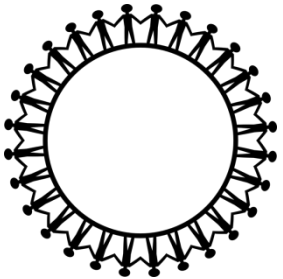


COMP-SAWP
coordinator
as link to EU network

COMP
peer review



COMP PA
working group



COMP

more expertise, better peer-review and more time for critical discussion

Take home messages

- ✓ Orphan designation can be requested for free at any stage of development
- ✓ Orphan legislation sets out criteria and incentives
- ✓ European Commission Decision gives access to incentives
- ✓ Concept of "significant benefit"
- ✓ Significant benefit must be demonstrated by data
- ✓ Invitation to seek early regulatory dialogue with COMP via protocol assistance procedure

References (in order of appearance)

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Any questions?

Further information

matthias.hofer@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
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