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Conflicts of interest: none

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The demonstration of significant benefit in the EU framework

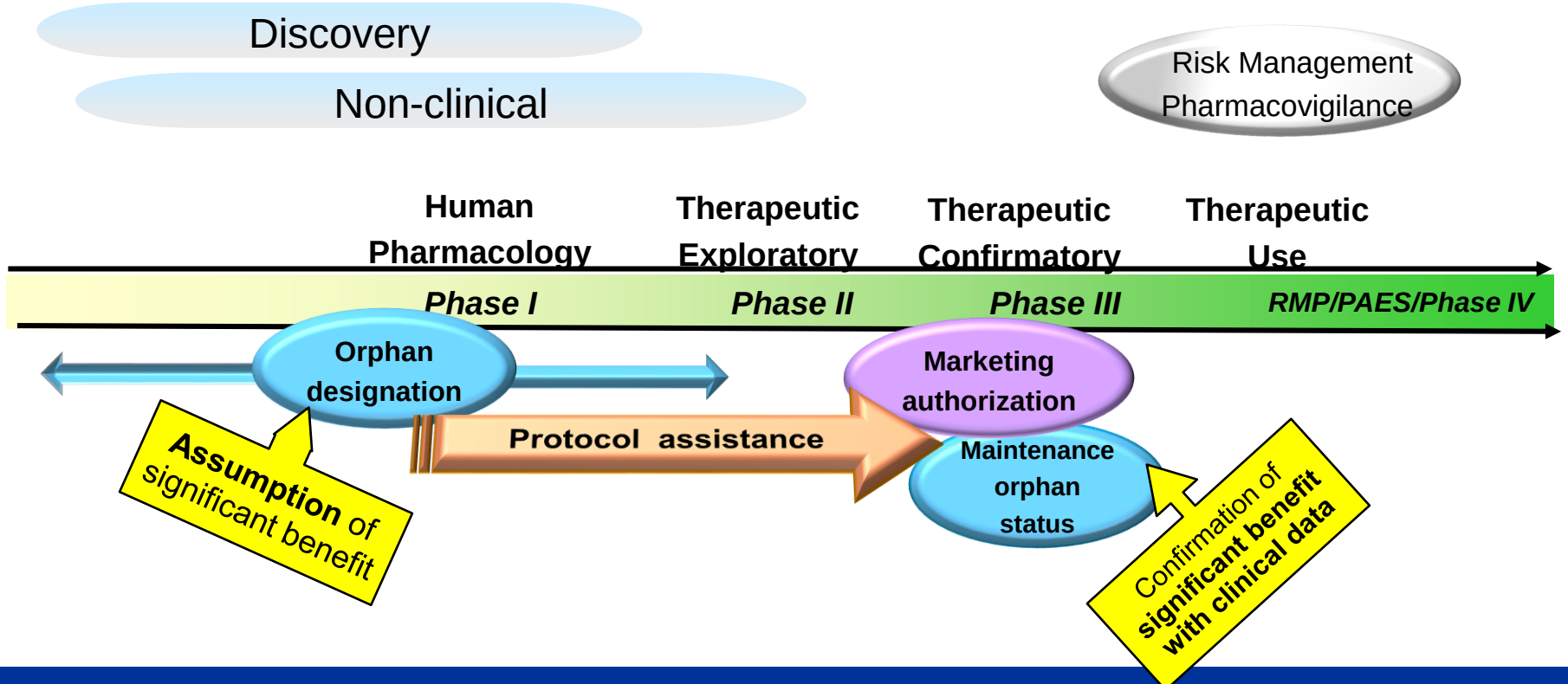
Laura Fregonese MD, PhD, Clin Epi (MSc), EMDM

XI FORESIGHT TRAINING COURSE
Changes in Regulatory Sciences in the EU
Pavia, 27 October 2018

Significant benefit

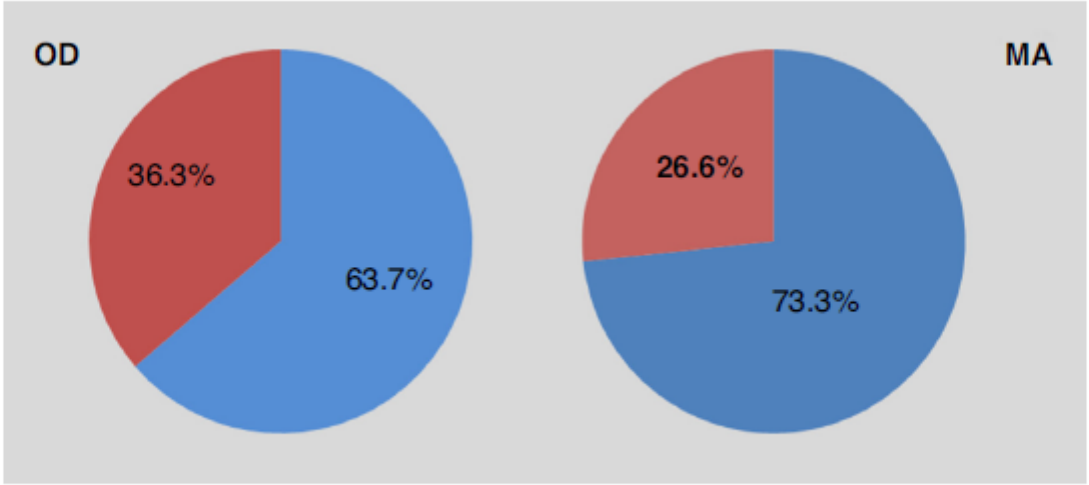
- Created with orphan regulation in the EU
- Initially envisioned as 'clinical superiority
- "***a clinically relevant advantage***" (e.g. better efficacy, better safety, better outcome as add-on) or "***a major contribution to patient care***" (e.g. more convenient dosing schedule, administration route)
- To be demonstrated in relation to all **satisfactory methods** for a condition (authorized medicines and SoC non-pharmacological methods)
- Commission Notice from 2016 introduces magistral formulations as potential satisfactory methods

Orphan status in the EU regulatory system



Orphan products requiring SB demonstration (2000-2015)

n = 1607



n = 147

How does the COMP assess significant benefit?

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

ELSEVIER

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

Reviews • KEYNOTE REVIEW

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

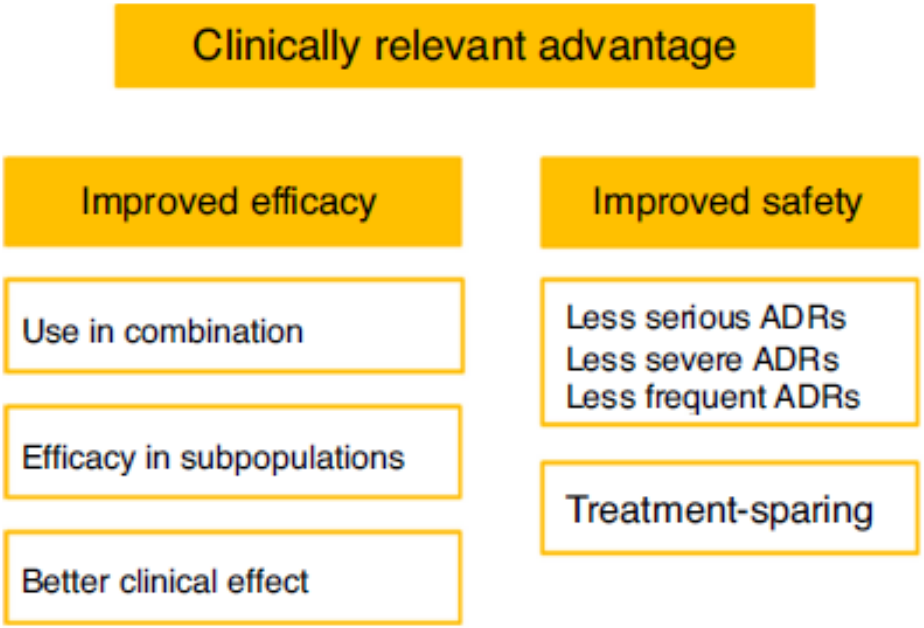
Laura Fregonese[1], Lesley Greene[2], Matthias Hofer[1], Armando Magrelli[3], Frauke Naumann-Winter[4], Kristina Larsson[1], Maria Sheean[1], Violeta Stoyanova-Beninska[5], Stelios Tsigkos[1], Kerstin Westermark[6] and Bruno Sepodes[7]

[1] European Medicines Agency (EMA), London, UK
[2] European Organisation for Rare Diseases (EURORDIS)
[3] Istituto Superiore di Sanità, Rome, Italy
[4] Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany
[5] College ter Beoordeling van Geneesmiddelen, Utrecht, The Netherlands
[6] (formerly of) Läkemedelsverket, Uppsala, Sweden
[7] Universidade de Lisboa, Faculdade de Farmácia, Lisboa, Portugal

Laura Fregonese, MD PhD MSc EMDM, is a Scientific Officer working in the Orphan and Pediatric Office at the European Medicines Agency as a specialist in clinical immunology and respiratory medicine. She is the lead for projects on the significant benefit of orphan medicines. Before joining the EMA she was involved as an academic and member of the EU Rare Diseases Task Force in the creation of health policies in the field of rare diseases, including the European Commission Communication on Rare diseases: Europe's challenges and the Recommendations and Guidance for Rare Diseases National Plans.

Kerstin Westermark, MD PhD, is currently retired from the Medical Products Agency in Sweden where she was Senior Expert and Endocrinologist. She was also appointed Adjunct Professor of Medicine at Uppsala University (Sweden), dedicating part of her time to research on Wilson's disease and teaching. She was the Chairperson of the European Medicines

Clinically relevant advantage



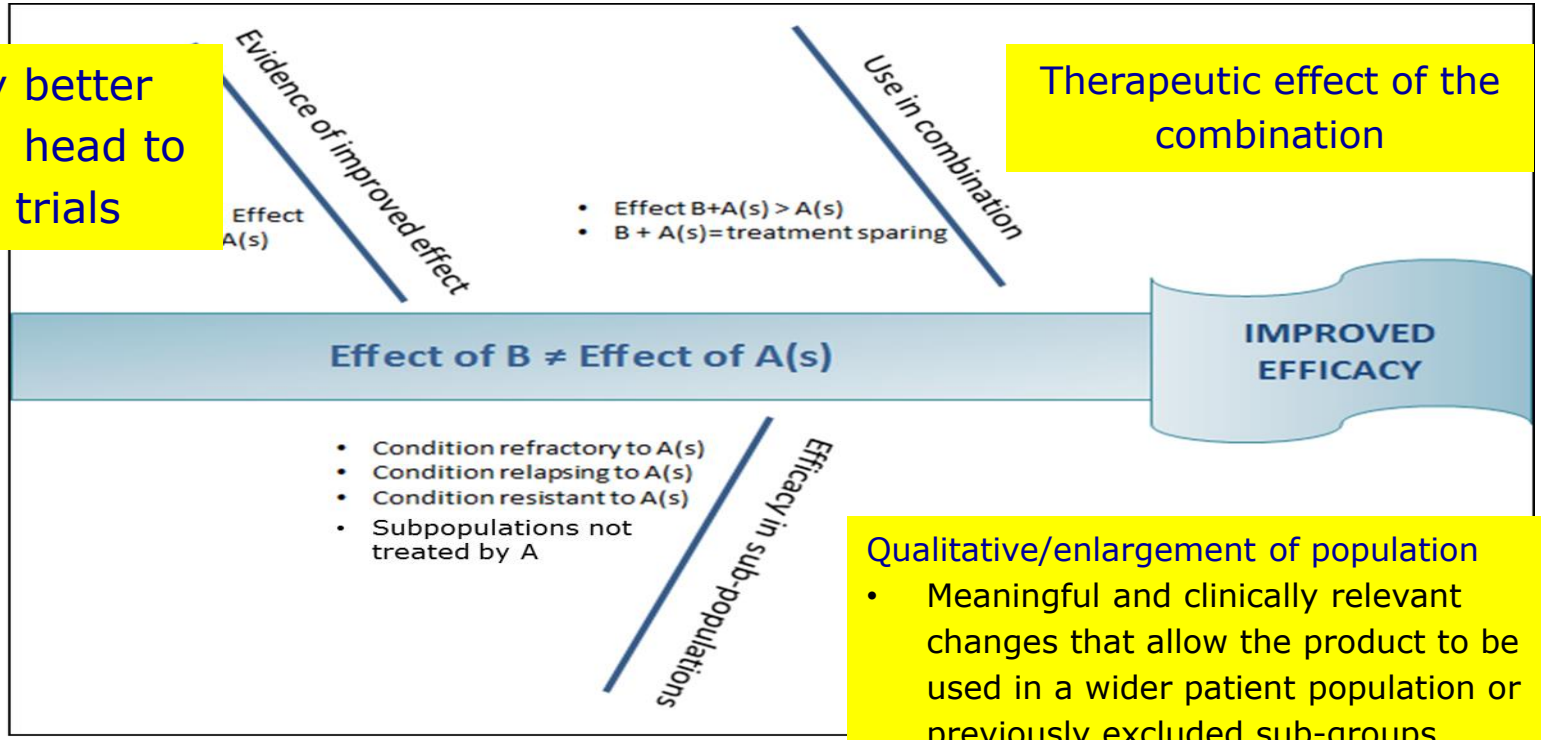
Favorable PK and/or PD OD

(new/alternative)

Mech of Action

Improved efficacy

Ideally better efficacy head to head trials



Therapeutic effect of the combination

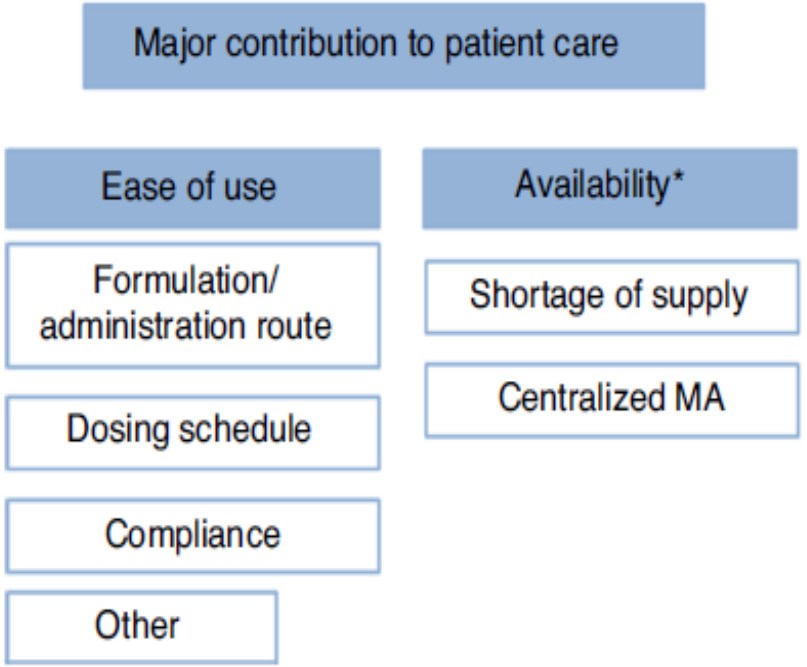
Qualitative/enlargement of population

- Meaningful and clinically relevant changes that allow the product to be used in a wider patient population or previously excluded sub-groups

Major contribution to patient care

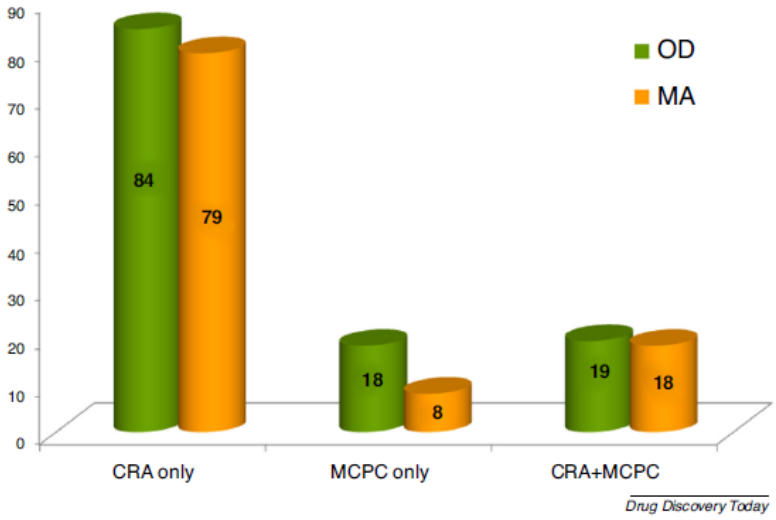
Theoretical examples

- 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)



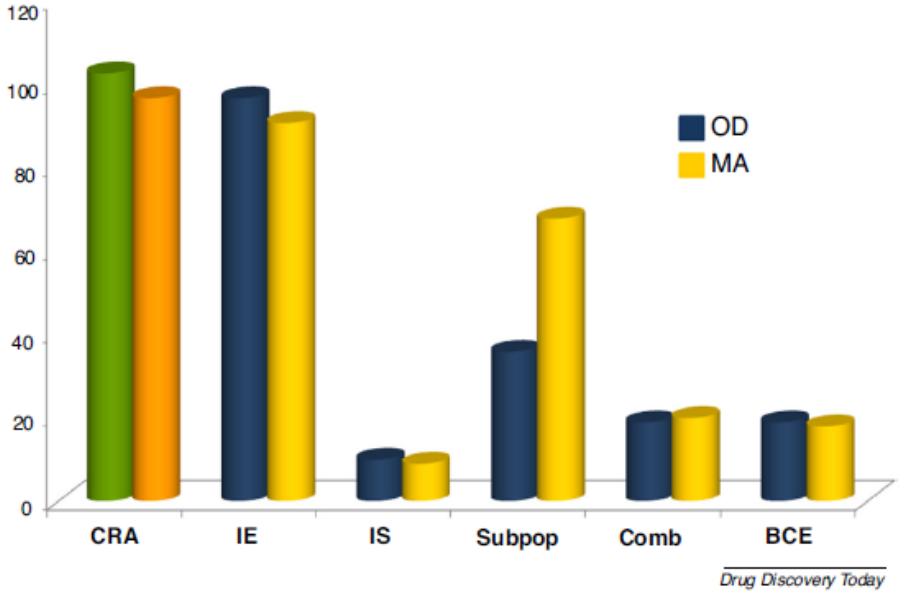
Favorable PK and/or PD OD

Frequency of grounds of significant benefit



- Lower number of grounds at MA linked to medicinal products that withdrew orphan status after SB was questioned by the COMP
- all products that lost orphan status at MA but one lost it because of lack of demonstration of SB
- grounds of MCPC granted as stand alone only in 8 cases at MA, from 18 cases that had acceptable assumptions at OD

Grounds of clinically relevant advantage



- Efficacy in Subpop:"*improving outcome for a sub-population in which there is no authorised treatment available, or in which currently existing treatment methods are non-suitable, or where the disease is resistant, refractory, or re-lapsing to existing methods*".
- Subpops need to be plausible from a medical and regulatory point of view, and established in the scientific literature and clinical practice (e.g. second line cancer tt)

Type and level of evidence

Hypothetical orphan at review- 1

Orphan X 2. line	Satisfactory Method (SM) 1-3	Product A - SB required!
Scientific evidence	**SM1**: SoC 1. line **SM2**: SoC 2. line **SM3**: notoriously limited efficacy	**Active-controlled trial vs SM2** Primary endpoint PFS **HR=0.31** OS numerical benefit
Inclusion criteria		relapse after treatment with SM1

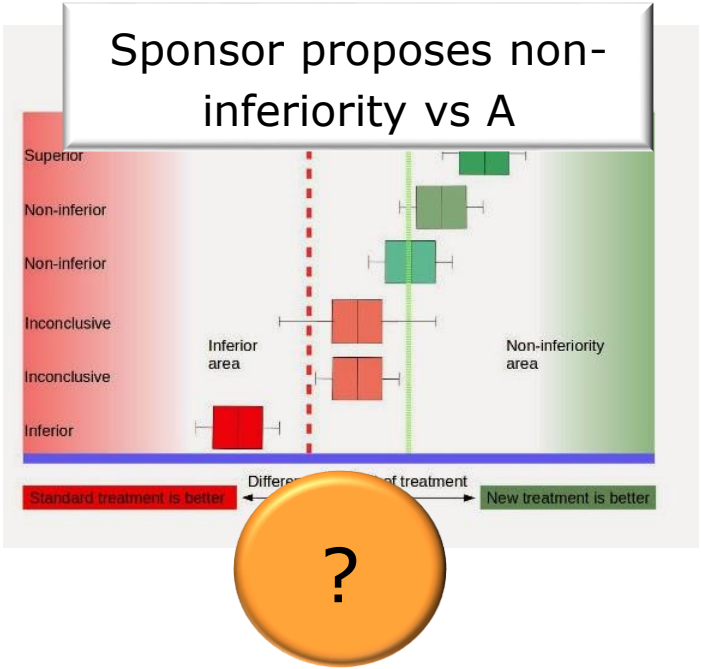
Challenges in advising on significant benefit

- **Existing products**

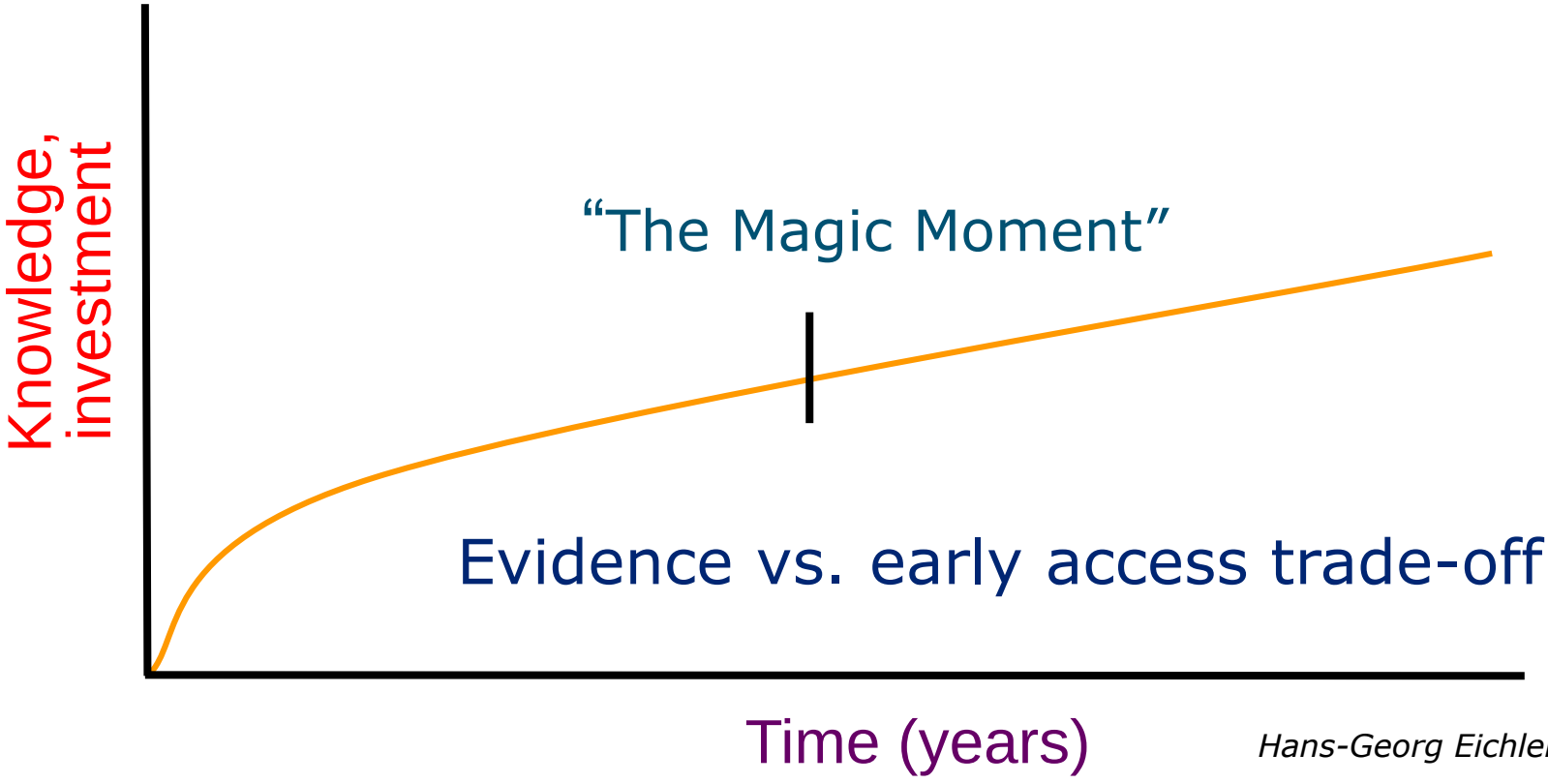
A = good efficacy of clinical manifestations X (indication: whole condition)

B = acceptable efficacy on clinical manifestations X; some control of manifestations Y (indication: whole condition)

- **new product:** possible better efficacy than B on manifestations X
- Potential to be used in the whole condition
- How to demonstrate IMPROVED EFFICACY?

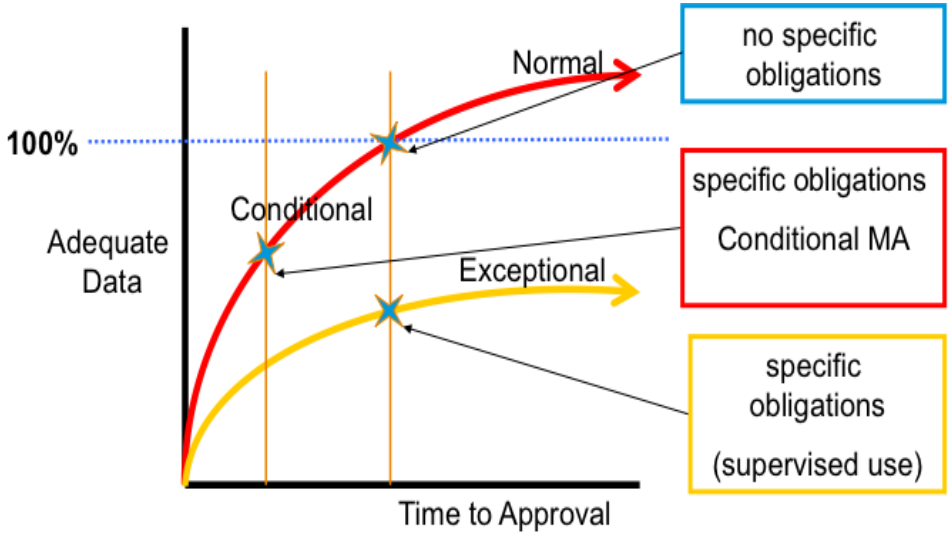


The binary nature of drug regulation



Hans-Georg Eichler, EMA

Evidence vs. early access trade-off



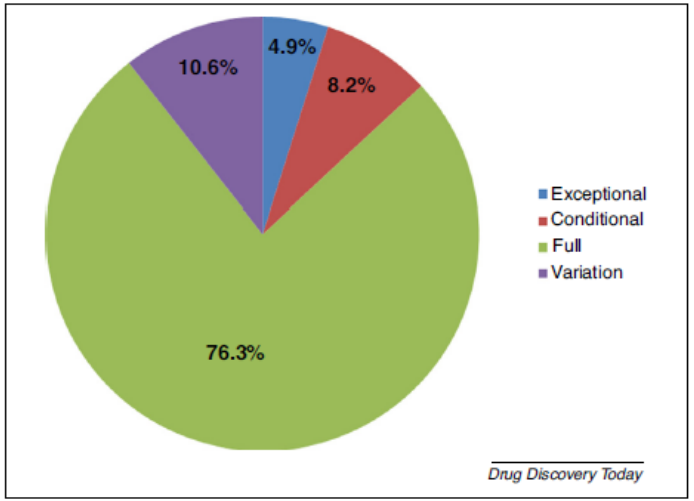
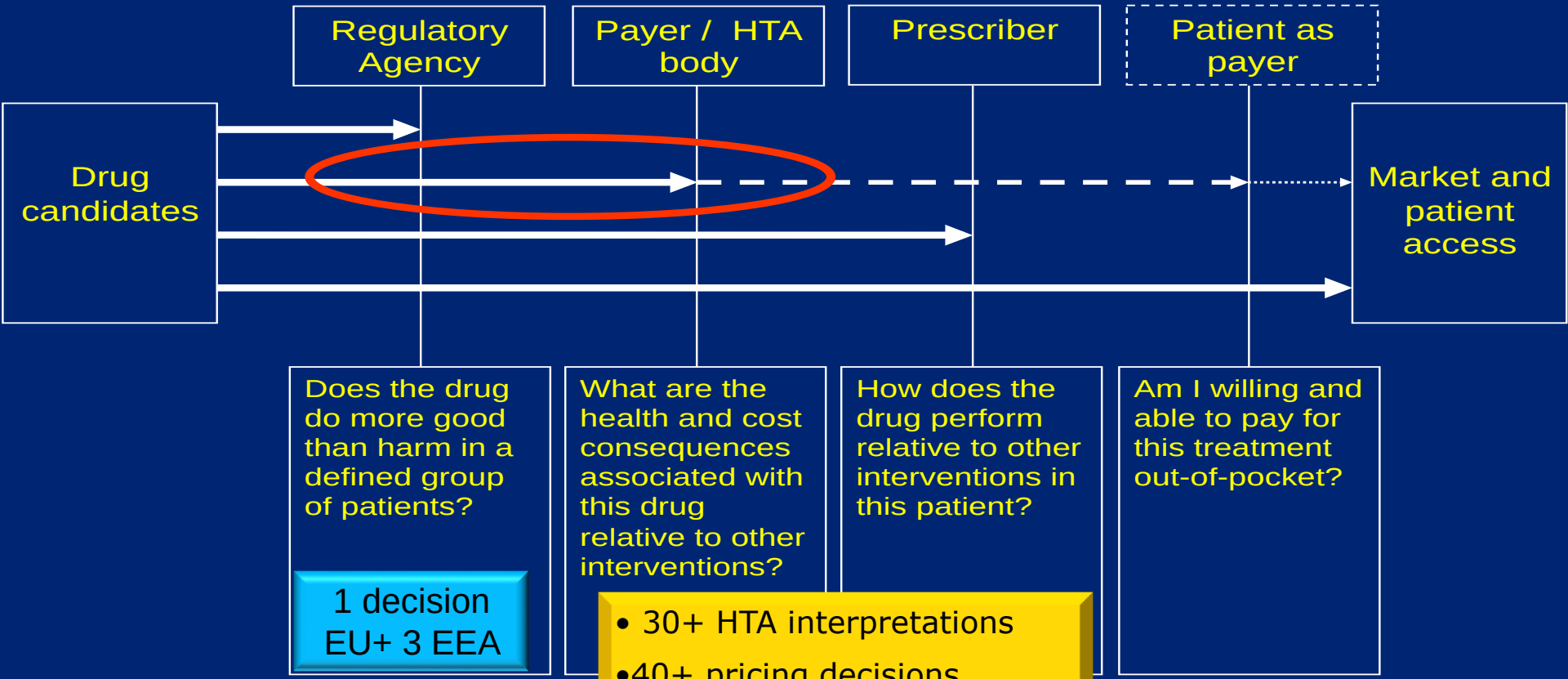


FIGURE 3

Authorized products with orphan status requiring demonstration of Significant Benefit (SB), distributed by type of Marketing Authorization (full MA, conditional MA, exceptional circumstances and variation).

Common problems in comparative efficacy/effectiveness

Decision makers on the road to market access



Nature Rev Drug Disc, 2010

Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs

Cataloguing FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders

by Frank J. Sasinowski, M.S., M.P.H., J.D.[1]
Chairman of the Board
National Organization for Rare Disorders

Small populations methodology

GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS

TABLE OF CONTENTS

Conditional MA

1.1 Justification that the medicinal product falls within the scope of the conditional marketing authorisation

The applicant should justify that the medicinal product falls within the scope of the conditional marketing authorisation regulation. The categories of medicinal products that fall within the scope of the conditional marketing authorisation regulation are defined in Article 2 of Commission Regulation (EC) No507/2006. These are products for human use falling under Article 3(1) and (2) of Regulation (EC) No 726/2004, and belonging to at least one of the following categories:

1. Seriously debilitating diseases or life-threatening diseases

The severity of the disease, i.e., its seriously debilitating, or life-threatening nature needs to be justified, based on objective and quantifiable medical or epidemiologic information. Whereas a life-threatening disease is relatively easy to describe based on figures of mortality, justifying that a disease is seriously debilitating will have to consider morbidity and its consequences on patients' day-to-day functioning. These aspects should be quantified in objective terms, as far as possible. Furthermore, serious debilitation, or fatal outcome should be a prominent feature of the target disease and therapeutic indication.

2. Medicinal products to be used in emergency situations

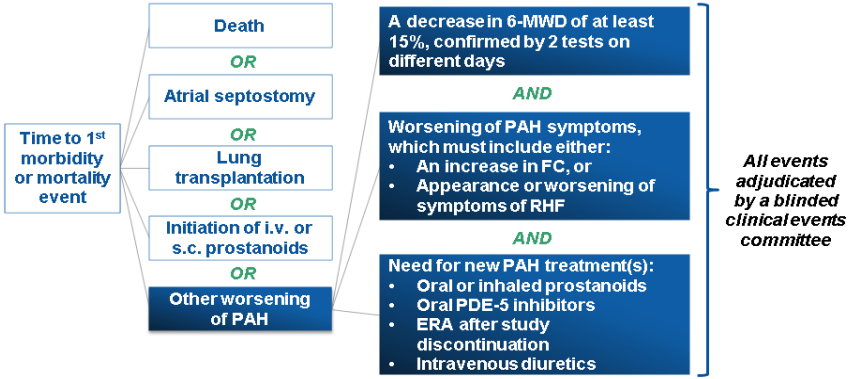
A justification should be provided that the medicinal product is intended for use in emergency situations, in response to public health threats duly recognised either by the WHO or by the Community (Decision No. 2119/98/EC). A reference to the relevant WHO Resolution or Decision, or to the measures adopted by the Commission in the framework of Council and Parliament Decision No. 2119/98/EC should be provided.

3. Orphan medicinal products

For requests submitted in accordance with article 2 (3) of Commission Regulation (EC) No. 507/2006, a copy of the Commission Decision on the designation as an orphan medicinal product should be provided.

Dual Endothelin receptor antagonist (ETA, ETB) treatment of PAH

- Monotherapy/combination, long-term treatment in adults WHO Functional Class II- III. Efficacy shown in idiopathic and heritable PAH, PAH associated with connective tissue disorders, and associated with corrected simple congenital heart disease
- multi-centre, randomised, double-blind, event-driven Phase 3 placebo controlled study on top of SoC (prostanoids and PDE4 inhibitors); 742 patients 3 tt groups
- **Primary endpoint:** first morbidity-mortality event up to end-of-treatment
- decreased risk of first morbidity and mortality event versus placebo: 45% higher dose group (HR 0.55); 30% (HR 0.70) in lower dose group
- Benefit vs other ERAs?



Endpoints?

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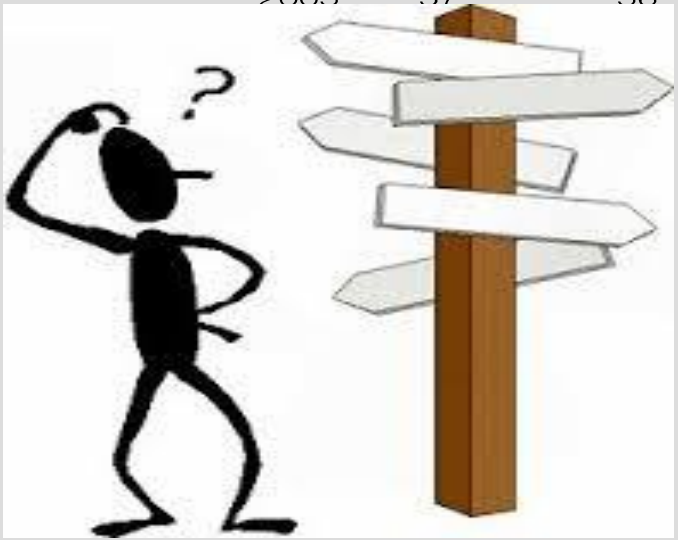
Drug	Trial acronym	Year	Study duration weeks	Subjects n	Primary end-point	Result
Interferon-γ		2004	58	330	PFS	No effect [28]
Pirfenidone		2005	36	107	Change in lowest 6MWD SpO_2	Reduced acute exacerbations [27]
Warfarin		2005	57#	56	Survival time	Improved survival [30]
N-acetylcysteine					Change in VC	Reduced progression [29]
Bosentan					Change in 6MWD	No effect [35]
Etanercept					Change in FVC and D_{LCO}	No effect [31]
Interferon-γ					Survival time	No effect [32]
Pirfenidone					Change in VC	Reduced progression [34]
Imatinib					Time to disease progression	No effect [33]
Sildenafil					>20% increase in 6MWD	No effect [46]
Bosentan					Time to IPF worsening	No effect [47]
Pirfenidone					Change in % pred FVC	Reduced progression [36]
Nintedanib (BIBF1120)					Rate of FVC decline	Trend to reduced progression [48]
Prednisolone+ azathioprine					Change in FVC	Increased mortality [49]
Warfarin					PFS	Increased adverse events [50]
Thalidomide		2012	24	24	Cough questionnaire	Reduced cough [51]
Ambrisentan	ARTEMIS	2013	35#	492	Time to disease progression	No effect [52]
Septrin	TUPAC	2013	52	118	Change in FVC	No effect [53]



PFS: progression-free survival; 6MWD: 6-min walking distance; SpO_2: arterial oxygen saturation measured by pulse oximetry; VC: vital capacity; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; #: median follow-up.

Major contribution to patient care

- Data for MCPC collected in pivotal trials for orphan MA often sub-optimal (non validated instruments, limited data-sets)
- Role of PROs? Core outcome measures vs. subjectivity
- Balance between generation of instruments for large number and heterogeneous rare diseases and case by case decisions on self-evident advantages as base of SB? (oral vs. IV, portability)
- How to quantify ease of administration, convenience, less monitoring needs, etc…
- Which role and methodology of patient preferences?
- Is there such a thing as an obvious improvement? Which cases do we need robust data?

Role of indirect comparison?

- Regulatory system uses seldom indirect comparisons
- More and more often proposed by applicants
- Requires in-depth assessment of models and modelling and simulation expertise
- What factors can influence whether indirect comparisons provide enough robustness to demonstrate significant benefit?
- Which data are the most relevant?
- Any role of registry data? (one case used for SB demonstration: positive)

Clinical benefit scales

- Created by oncology scientific societies; usually based on MA clinical trials
- ASCO: value combination of clinical benefit, side effects, and improvement in symptoms/quality of life in the context of cost
- ESMO: relative benefit assessed on survival, QoL, surrogate outcomes for survival/QoL or treatment toxicity

J Clin Oncol. 2017 Aug 20;35(24):2764-2771. doi: 10.1200/JCO.2016.71.6694. Epub 2017 Jun 2.

Do the American Society of Clinical Oncology Value Framework and th
Medical Oncology Magnitude of Clinical Benefit Scale Measure the San
Benefit?

Cheng S[1], McDonald EJ[1], Cheung MC[1], Arciero VS[1], Qureshi M[1], Jiang D[1], Ezeife D[1], Sabharwal M[1], Chambers A
Chan KKW[1].

- Obtaining an objective assessment of clinical benefit satisfying all stakeholders is unrealistic.
- Three major perspectives (patients, doctors and public health) can be identified.
- The ASCO framework of clinical benefit takes the patients perspective.
- The ESMO scale takes a public heath perspective.

Significant benefit across provisions

- 'significant clinical benefit' (for an additional year of marketing protection)

  Article 14(11) of Regulation (EC) No 726/2004)

- 'significant benefit' (for orphan designation)

  Article 3.1(b) of Regulation (EC) No 141/2000

- 'clinical superiority' (for derogation from orphan market exclusivity)

  Article 8(3) of Regulation (EC) No 141/2000

- 'significant therapeutic benefit' (for PIP waiver)

  Article 6(2) and 11.1(c) of Regulation (EC) No 1901/2006

- significant differences in efficacy and safety (for NAS)

  Article 10(2) of Directive 2001/83/EC

- 'major therapeutic advantage' (for a conditional marketing authorisation)

  Article 4 of Regulation (EC) No 507/2006

- 'major public health interest' (for accelerated assessment)

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

"Benefits" of (orphan) medicines

Therapeutic advantage

Significant benefit

Significant therapeutic benefit

Clinical added value

Cost-effectiveness

Added (therapeutic) value

EMA-HTA collaboration

- Early dialogue/scientific advice
- "Late dialogue"/peri-licensing advice
- Information exchange
- Methodologies to identify the treatment eligible population
- Significant benefit vs. added therapeutic value
- Unmet medical need and therapeutic innovation
- Patient and clinician engagement
- Methodological approa dy designs
- Population-specific or Intervention-specific areas

>100 parallel EMA – HTA SA procedures with EU HTA bodies from UK, Italy, Germany, Sweden, France, Netherlands, Spain, Belgium, Austria, Poland, Norway, Hungary

Discussion?

- **E**ffect size (e.g. cancer relapsing/refractory to previous treatments)
- **W**hich comparators?
- Quantification of "unquantifiable" endpoints/self-evident advantages?
- Quality of life?
- Caveat when advantage linked to device
- Lack of "conditional" significant benefit in case of conditional approval
- Which use of indirect comparisons? (inter-trials, network analysis, registry data, etc)

Thank you for your attention

Further information

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