Significant benefit:

origins and experience up to date

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Kerstin Westermark

Member of COMP and SAWP

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Topics

- Some fundamental articles
- ‘Significant Benefit’ and the ‘Spirit of the Orphan Regulation’
- Regulations, guidelines and recommendations; Definitions and Concepts
- COMP review procedure at marketing authorisation application (MAA) and Market Exclusivity (ME)

REGULATION (EC) No 141/2000
Some fundamental Articles

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REGULATION (EC) No 141/2000

Article 3

Criteria for designation

1. A medicinal product shall be designated as an orphan
•medicinal product if its sponsor can establish:
1 (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

REGULATION (EC) No 141/2000

Article 8

Market exclusivity

•1. Where a marketing authorisation in respect of an orphan medicinal product is granted …the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.
•2. - .. - ..”10 years can be reduced …to six years if, at the end of the fifth year it is established that the criteria laid down in Art. 3 are no longer met…
•3. … derogation from paragraph 1, and […], a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:
(c) the second applicant can establish in the application that the second medicinal product, **although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior**.

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Different concepts – but what was the *spirit* of the Regulation?

- significant benefit

- safer, more effective or otherwise clinically superior

Article 3 Criteria for Designation – Evolution of the 'Significant Benefit' criterion

ORIGINAL Commission proposal *Article 3*

1. A medicinal product shall be designated as orphan medicinal product if its sponsor can establish……..that there exists no satisfactory method……that has been authorised in the Community or, if such method exists, **that it can reasonably be expected that the medicinal product will be safer, more effective or otherwise clinically superior**.

AMENDED Commission proposal *Article 3*

1. A medicinal product shall be designated as orphan medicinal product if its sponsor can establish…. that there exists no satisfactory method……that has been authorised in the Community or, if such method exists, **that the medicinal product will be of significant benefit to those affected by the condition** ~~**that it can reasonably be expected that the medicinal product will be safer, more effective or otherwise clinically superior.**~~

AMENDED Commission proposal *Article 3*

From **EXPLANATORY MEMORANDUM**

2. Definitions for 'similar medicinal product" and "clinical superiority"

Since clinical superiority is difficult to establish at the very early stage of development when designation as an orphan medicinal product is likely to take place, this term has been removed from Article 3 and replaced by the notion that, in situations where there is already an existing treatment for an orphan condition, significant benefit to those affected by the condition should be demonstrated.

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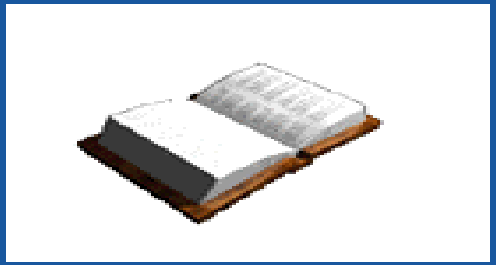

- **Regulation (EC) No 141/2000 on Orphan Medicinal Products**
- **Commission Regulation (EC) No 847/2000**
- **Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009 Final)**
- **Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another (ENTR/6283/00** *Revision 4, 2014***)**
- **Communication from the Commission on Regulation (EC) No 141/2000 on orphan medicinal products (2003/C 178/02)**
  Obs.! To be replaced by :Commission Notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on Orphan Medicinal Products) - currently in public consultation

’Significant Benefit’
in the context of the Orphan Regulation
is NOT:

- ***Benefit/Risk*** balance: (Assessed by CHMP at the time of Marketing Authorisation Application (MAA) in order to allow a recommendation for MA)

- **‘Significant *Clinical* Benefit’:** (One year extension of the 10 year marketing protection period if the Marketing Authorisation Holder obtains MA for one or more new therapeutic indications bringing a ‘significant clinical benefit’ in comparison with existing therapies)

- **‘Significant *Therapeutic* Benefit’: (**The Paediatric Committee considers whether or not any proposed studies can be expected to be of ‘significant therapeutic benefit’ to and/or fulfil a therapeutic need of the paediatric population)

Definition of Significant Benefit

Article 3 of Commission Regulation EC 847/2000

"A clinically relevant advantage or
a major contribution to patient care"

Guideline on the Format and Content…
ENTR/6283/00 *Revision 4*, 2014

At the time of Orphan Designation (OD):

•……, the sponsor should provide justification for the assumption of significant benefit where there already exist (EU) authorised (= satisfactory) medicinal products

•'Assumptions of potential benefit(s) should be plausible. Preclinical data and preliminary clinical information…

Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009 Final), cont.

At orphan designation (OD)

Sound pharmacological concept

Compelling evidence in relevant preclinical models

Unconvincing preliminary clinical data

Guideline on the Format and Content… ENTR/6283/00 *Revision 4*, 2014

At the time of Marketing Authorisation Application (MAA):

• At the time the application for Marketing Authorisation (MA) is reviewed by the CHMP, demonstrate significant benefit over currently authorised methods in order to maintain orphan status

•At this stage, the COMP will require a higher level of data/evidence for the orphan status than at the time of designation to be maintained

Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009 Final)

'…the COMP will evaluate whether there is a high probability for the patients to experience a clinically relevant benefit…it has to be concrete and based on the data contained in the application for marketing authorisation and the arguments presented by the sponsor'

Communication from the Commission on Regulation (EC) No 141/2000 on orphan medicinal products (2003/C178/02)

to be replaced by:
Commission Notice on the application of Articles 3,5 and 7 of regulation (EC) No 141/2000 on Orphan Medicinal Products (currently in public consultation)

"It is apparent from Article 3(1)(b) of regulation No 141/2000 and the spirit underlying the system established by that regulation that the criteria for finding of a significant benefit are strict. The purpose of the legislation is to encourage and reward innovative treatments. It implies an investment in research and development of the potential improved medicinal product that can bring meaningful advantages for the patients"
"Protocol assistance is recommended to ensure an appropriate clinical development …can also include guidance to demonstrate significant benefit…

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COMP review procedure at MAA

- Review in parallel to CHMP assessment
- Sponsor to provide report to COMP with data supporting the maintenance of orphan designation criteria
- COMP to check if orphan criteria still hold
- SB to be demonstrated at the first MA and irrespective of type of MA (No provisions for 'conditional' SB)
- SB to be demonstrated also in comparison with products authorised during the time period between OD and MA
- **If no evidence for significant benefit at the time of MA, the product will lose its OD but MA as a non-orphan product still possible (No obligation to repay incentives obtained)**

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10 (+2) years of Market Exclusivity - the strongest Incentive for the development of Orphan Drugs... (Reg. 141/2000, Art. 8(1)&(3)

Protection against:

- **similar products for same therapeutic indication**

Three derogations:

- the holder of the MA for the original orphan medicinal product has given his consent to the second applicant,

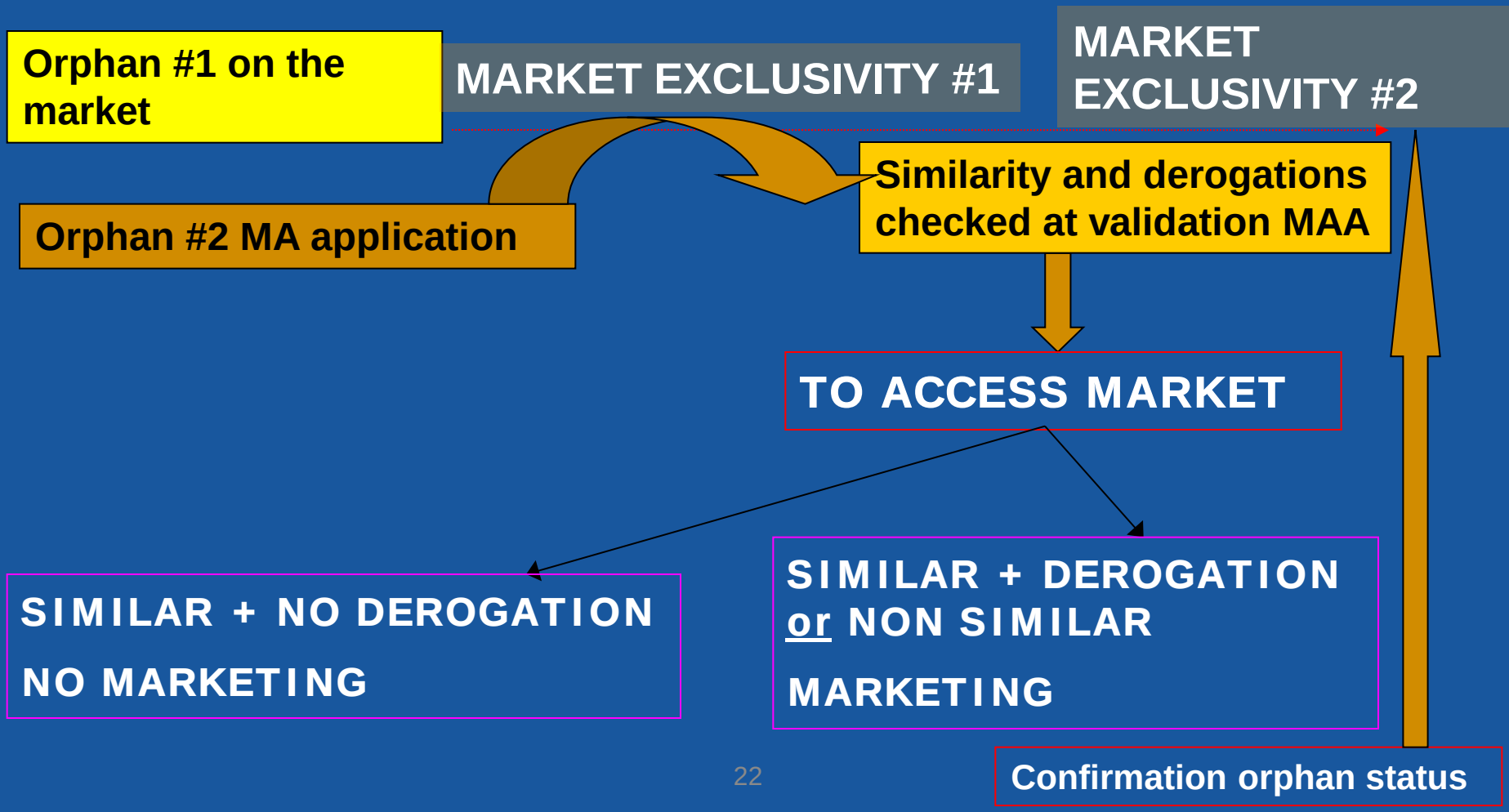
  or

- the holder of the MA for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product,

  or

- the second applicant can establish in the application that the second medicinal medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior

Market Exclusivity - Specific Requirements



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Conclusions

- Regulation aimed to reward products for same orphan indication only if 'better'
- **Different levels of evidence required at initial designation cf confirmation at marketing authorisation**
- **Initial-assumption of significant benefit**
- **Confirmation – establishment of significant benefit**
- **Onus on the sponsor to establish significant benefit**

Thank you for your attention!

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