Rare Disease Research Forum – Challenges and Solutions

KI, Febr. 21, 2011

'Support from the EMA/COMP'

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Why an EU Regulation on Orphan Drugs?

Extracts from EU Regulation 141/2000 on Orphan Medicinal Products:

"Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients";…such action is best taken at Community level in order to take advantage of the widest possible market and to avoid the dispersion of limited sources…"

But…

" the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions"

As…

"some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product… would not be recovered by the expected sales"

Incentives in EU for Orphan Medicinal Products

- **Market Exclusivity**
  - 10 years for all orphan medicines (from marketing authorisation)
  - + 2 years if results from paediatric studies included in the Marketing Authorisation Application
- **Fee Reductions** for product development
  - Application for Orphan Designation: free
  - Protocol assistance (=Scientific Advice) and follow up: free
  - Application for Marketing Authorisation: reduced fees (100% for Small and Mediumsized Enterprises (SMEs)
  - *+ Extended incentives for SMEs in post authorisation*
- **EU Marketing Authorisation** (unique centralised procedure)
- **Priority** to EU Research - Framework programs; FP7 (2007-13): RDs "FP7 priority"
- **National incentives (EC inventory)**

Incentives cont.
Market exclusivity - 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**

What is an Orphan Medical Condition?

EC Guideline (ENTR/6283/00)

- Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome)
- Development plausible based on pathogenesis and pharmacodynamics
- Distinct pathophysiology, histology, clinical presentation
- Different severities- stages not acceptable
- Special considerations: subsetting (exclusive action – not 'salami slicing'), intersection, treatment modality

What is an Orphan Medicinal Product? Definition/Criteria

Medicinal Products for treatment, diagnosis or prevention:

RARITY: for rare conditions (affecting not more than 5 in 10,000 persons in the Community)

OR

No return on investment: development costs > expected return on investment

Seriousness: life-threatening or chronically debilitating

No satisfactory (authorised) methods of treatment in the EU - or if existing, proposed orphan product should be of significant benefit to the patients suffering from the condition

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What is “Significant benefit”?

“A clinically relevant advantage or a major contribution to patient care”

- Based on assumptions at the time of orphan designation
- Significant benefit over authorised products (satisfactory)
- COMP to assess whether or not significant benefit assumptions are supported by available data/evidence supplied by applicant

Significant benefit to be confirmed prior to marketing authorisation to maintain orphan status

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Assumption of significant benefit - Examples

- Drug has a new mechanism of action
  - Efficacy will have to be demonstrated
  - Opens possibilities for drug combination
  - Therapeutic alternative
- Claims of better efficacy
- More convenient administration route (major contribution to patient care)
- Better safety
  - Most times complementary safety profile
  - Weak assumption for justification of significant benefit (data to support often lacking at the time of orphan designation application)

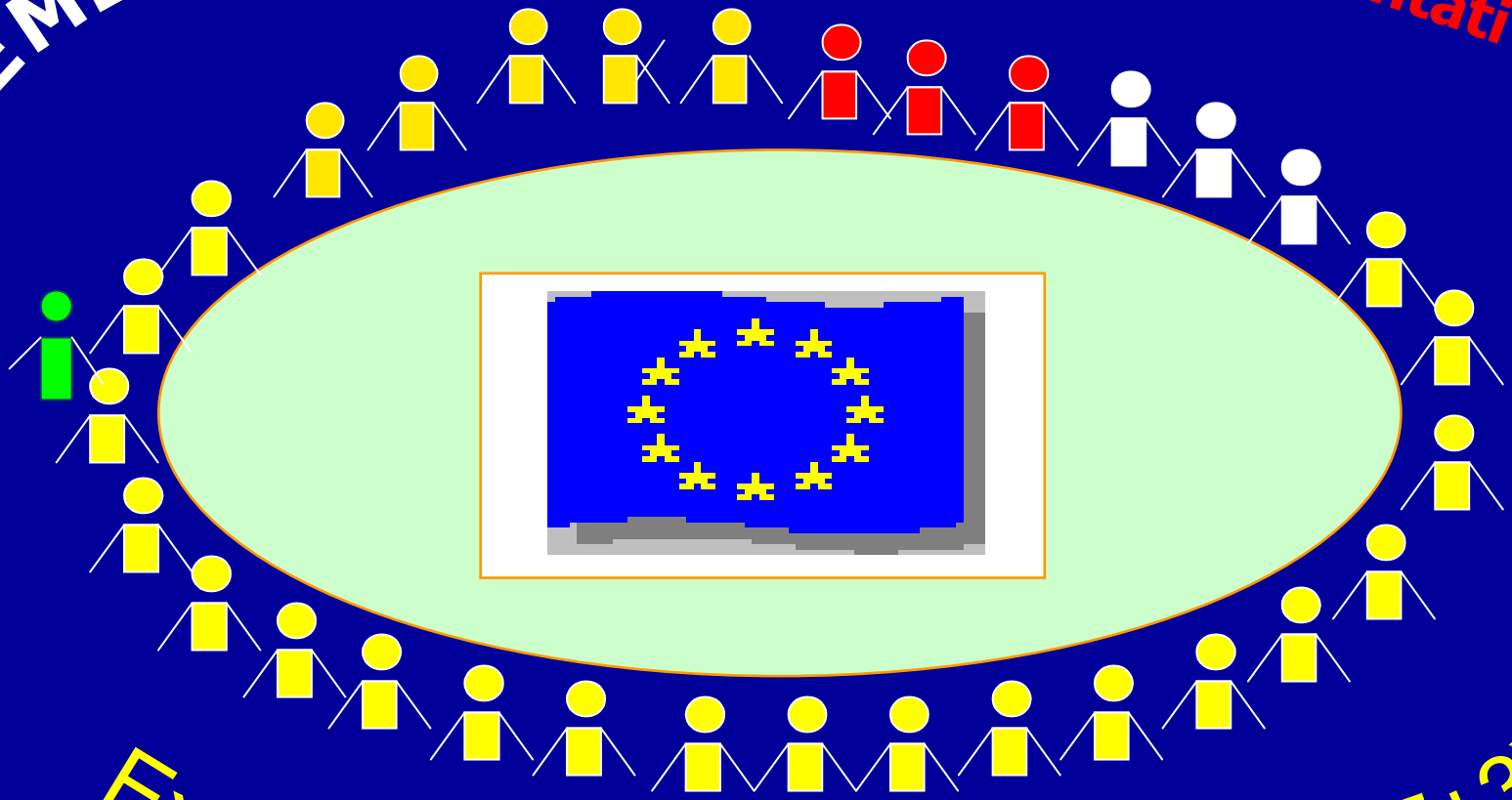
How to obtain orphan designation?

- Applications submitted to the EMA (European Medicines Agency) COMP (Committee for Orphan Medicinal Products) either by companies or individuals (sponsors)
  - Established in the EU
- Application form +
  - Description of the condition
  - Description of the medicinal product
- Prevalence calculation of the condition
  - Justification of severity
  - Justification of “significant benefit” (when applicable)
  - Description of product development (current and future)

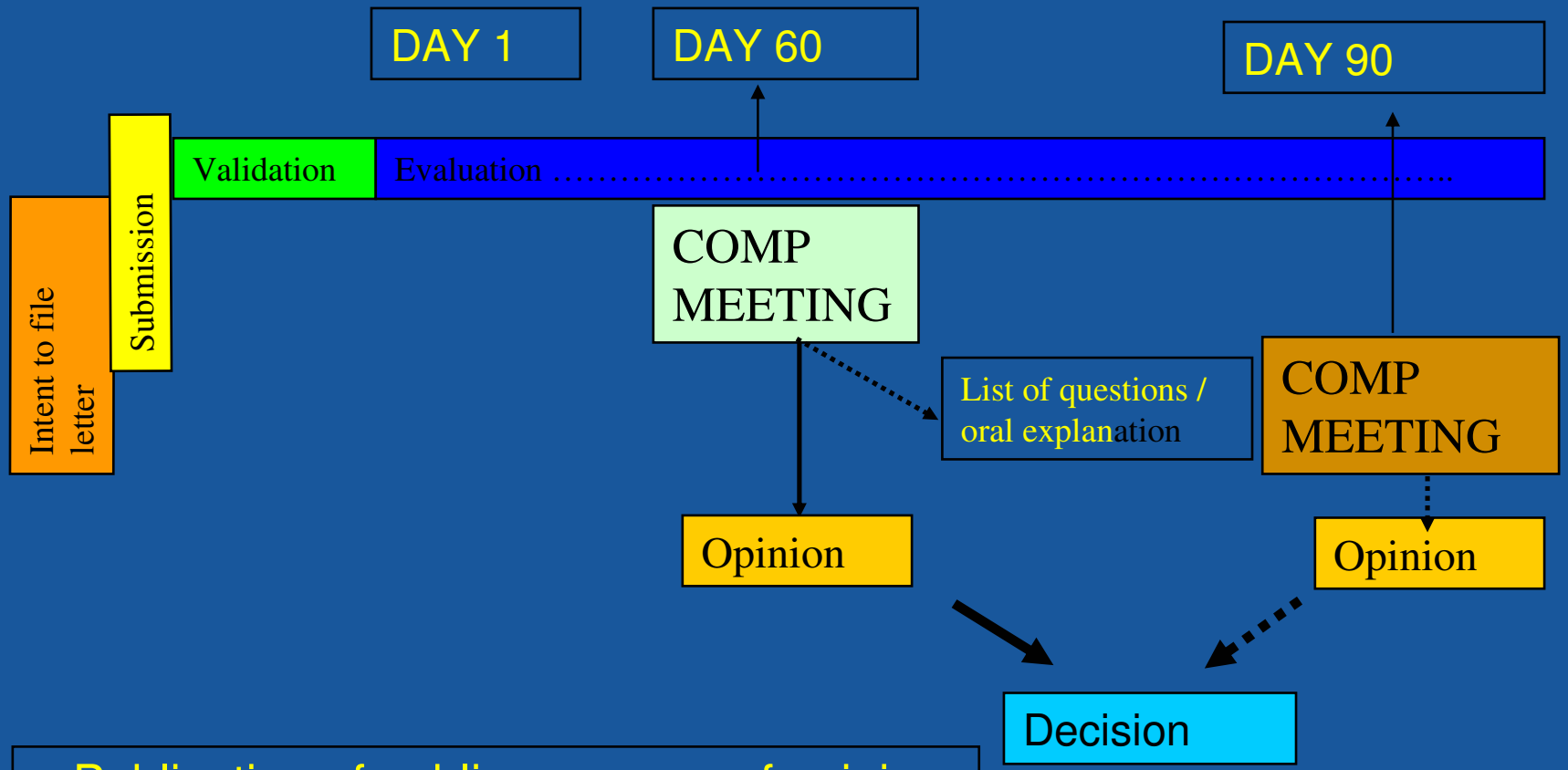
Committee for Orphan MPs

EMEA members (3)

Patients' representatives (3)



Experts from Member States (27+3)



- Publication of public summary of opinion (lay language) on EMA website

Incentives cont.
Protocol Assistance (PA)

Article 6 of Regulation (EC) No 141/2000

Protocol Assistance = Scientific Advice for companies developing Orphan Medicinal Products

Protocol Assistance (PA) – Key Features

- Systematic pre-submission meeting with the EMEA
- Discussion meetings in the majority of cases
- Additional and specific expertise to participate in Scientific Advice Working Party (SAWP)
- Significant Benefit issues – Responsibility of 3 COMP members of SAWP
- Follow-up PA possible
- Fee reduction (currently 100% = free!)

Scientific advice / protocol assistance - improved chances for a successful marketing authorisation application!

Orphan Drug development requires:

- Flexibility at Regulatory level
  - Potential for alternative approaches
- Strive for efficiency

But - No new methods for rare disorders

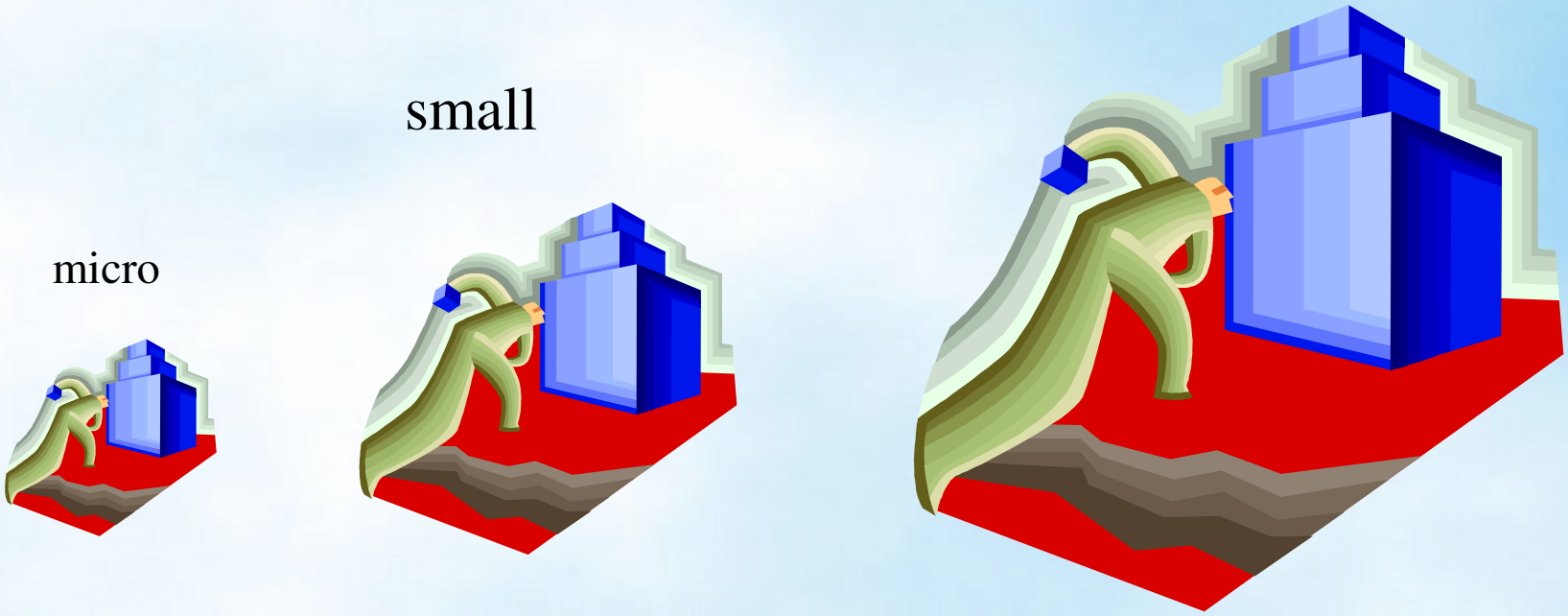
“SME Office”

for

& medium-sized enterprises

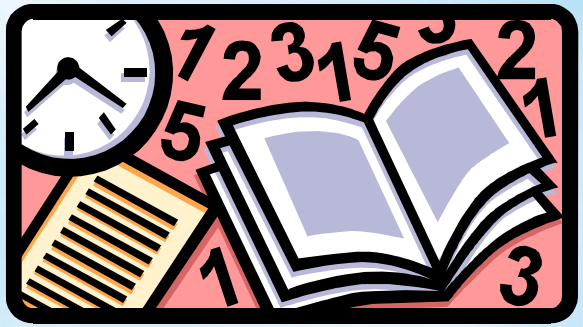
small

micro



Incentives for SMEs

- Administrative and procedural assistance
- Fee reductions
- Fee exemptions for certain administrative services
- Deferral of fee for application for marketing authorisation or inspection
- Conditional fee exemption
- Translation of product information



Definition of SME

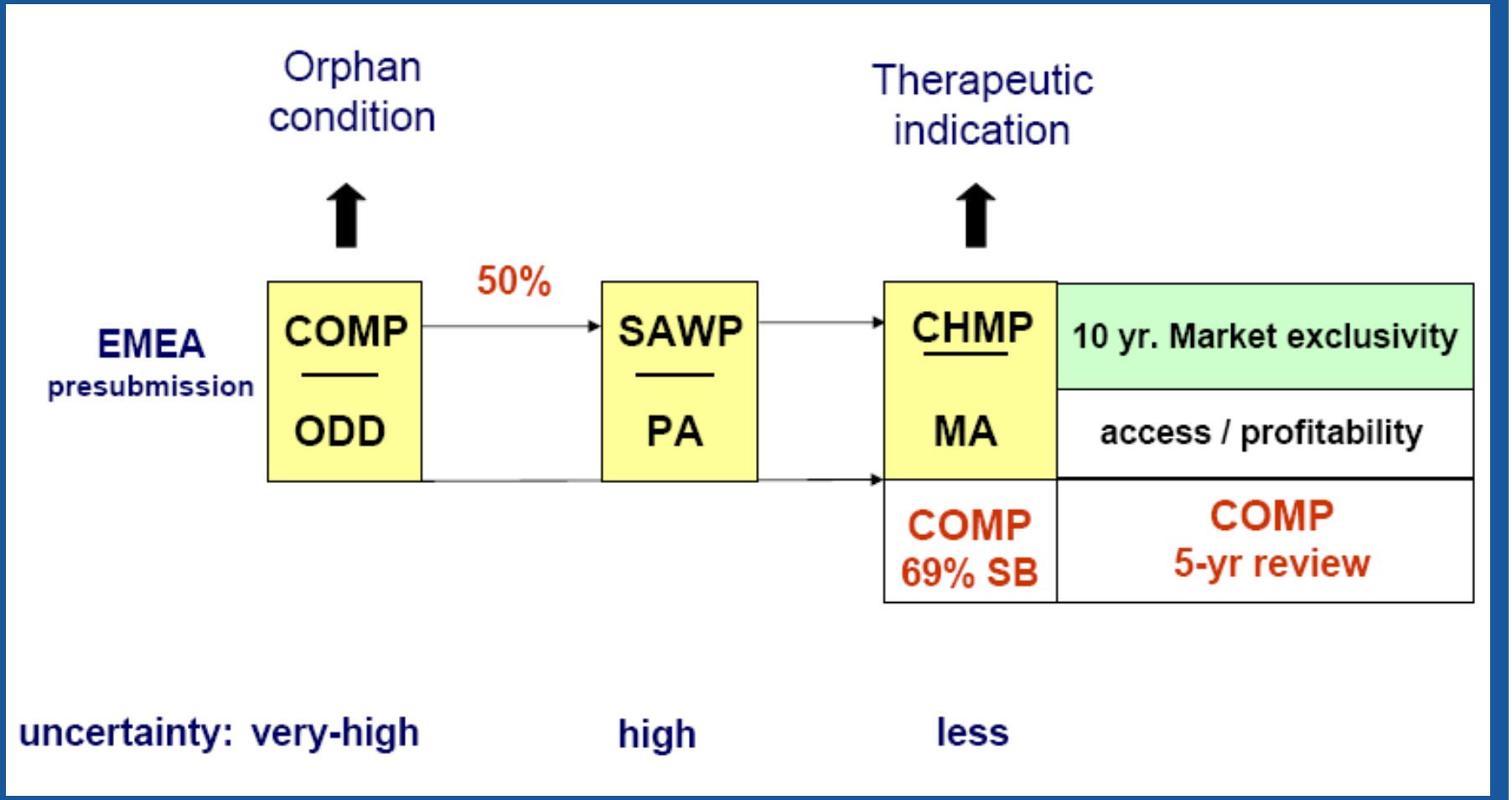
THE NEW THRESHOLDS *(Art. 2)*

Enterprise category	Headcount: Annual Work Unit (AWU)	Annual turnover	or	Annual balance sheet total
Medium-sized	< 250	≤ €50 million (In 1996 € 40 million)	or	≤ €43 million (In 1996 € 27 million)
Small	< 50	≤ €10 million (In 1996 € 7 million)	or	≤ €10 million (In 1996 €5 million)
Micro	< 10	≤ €2 million (previously not defined)	or	≤ €2 million (previously not defined)

Website

E-mail queries: smeoffice@ema.europa.eu

From Orphan Status to Marketing authorisation



www.ema.europa.eu

Thank you for your attention!

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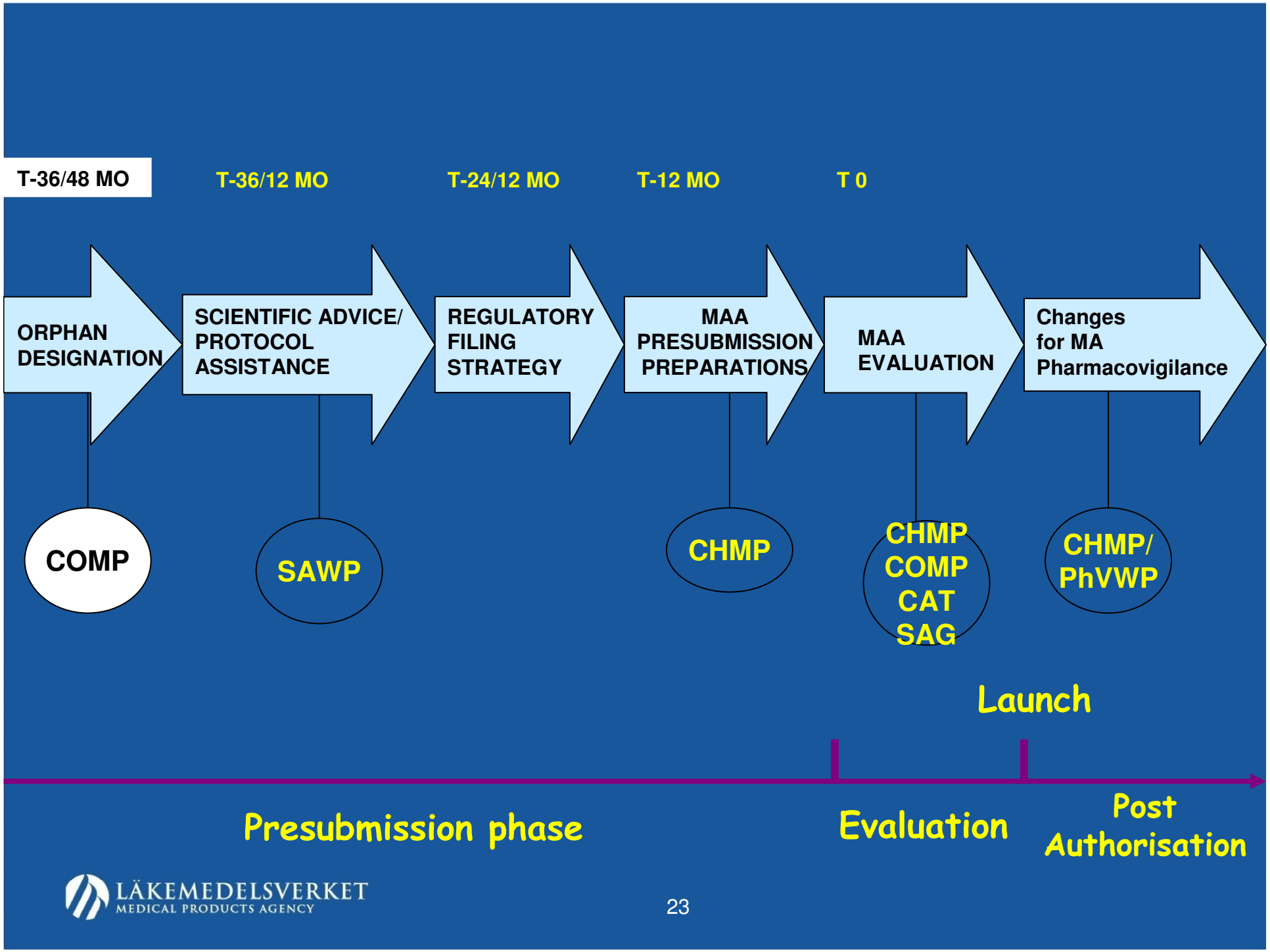
Back-up slides


T-36/48 MO
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ORPHAN DESIGNATION
SCIENTIFIC ADVICE/ PROTOCOL ASSISTANCE
REGULATORY FILING STRATEGY
MAA PRESUBMISSION PREPARATIONS
MAA EVALUATION
Changes for MA Pharmacovigilance
COMP
SAWP
CHMP
CHMP COMP CAT SAG
CHMP/ PhVWP
Launch
Presubmission phase
Evaluation
Post Authorisation

RD/OD research, development and bringing to the market of is profitable business for Member States

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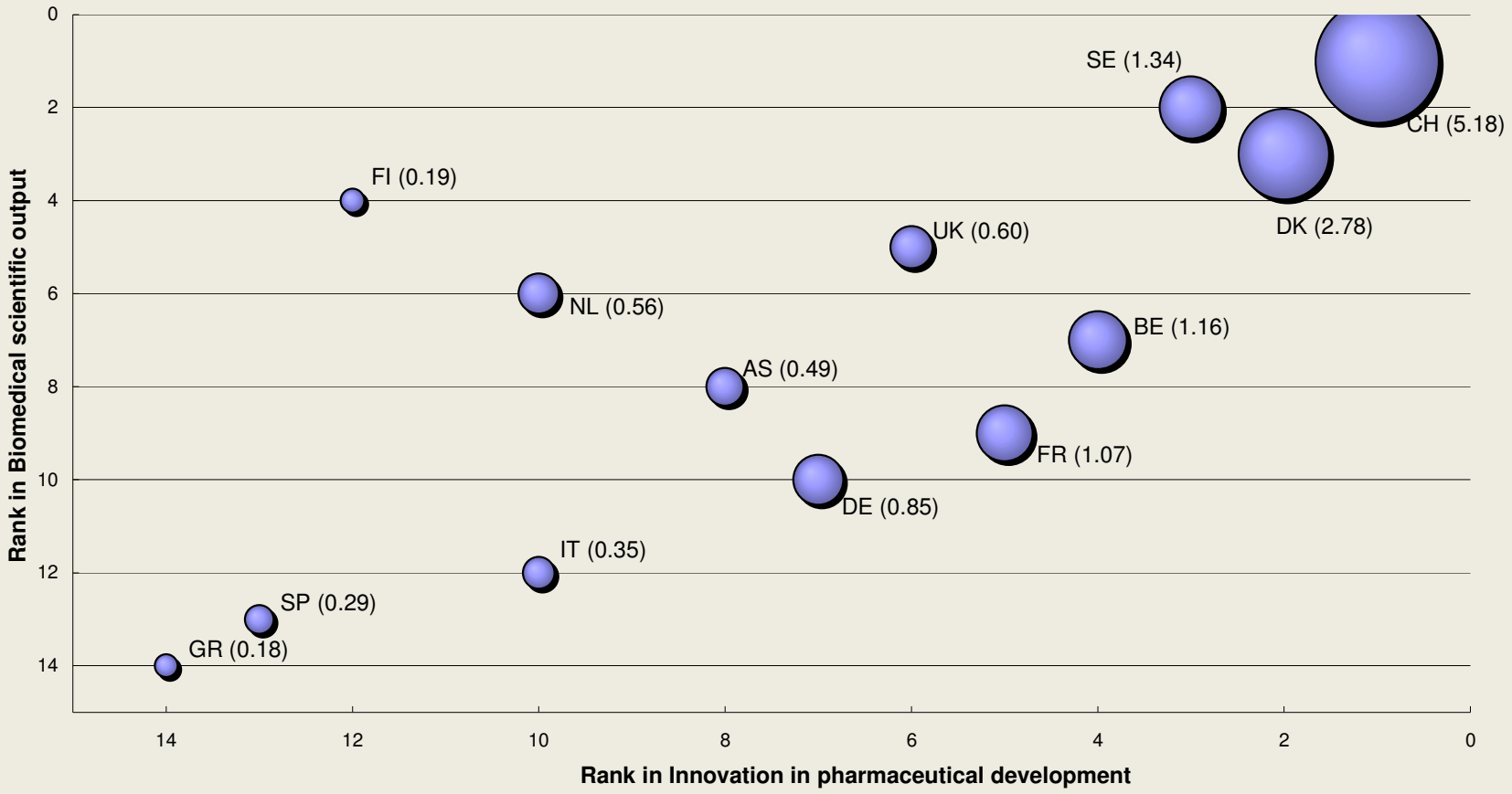
Biomedical scientific output, innovation in pharmaceutical development and orphan designations in Europe

From Heemstra et al, Drug Discov. Today, 2008;13(15-16):670-6.



Status of Orphan Marketing Authorisation Applications

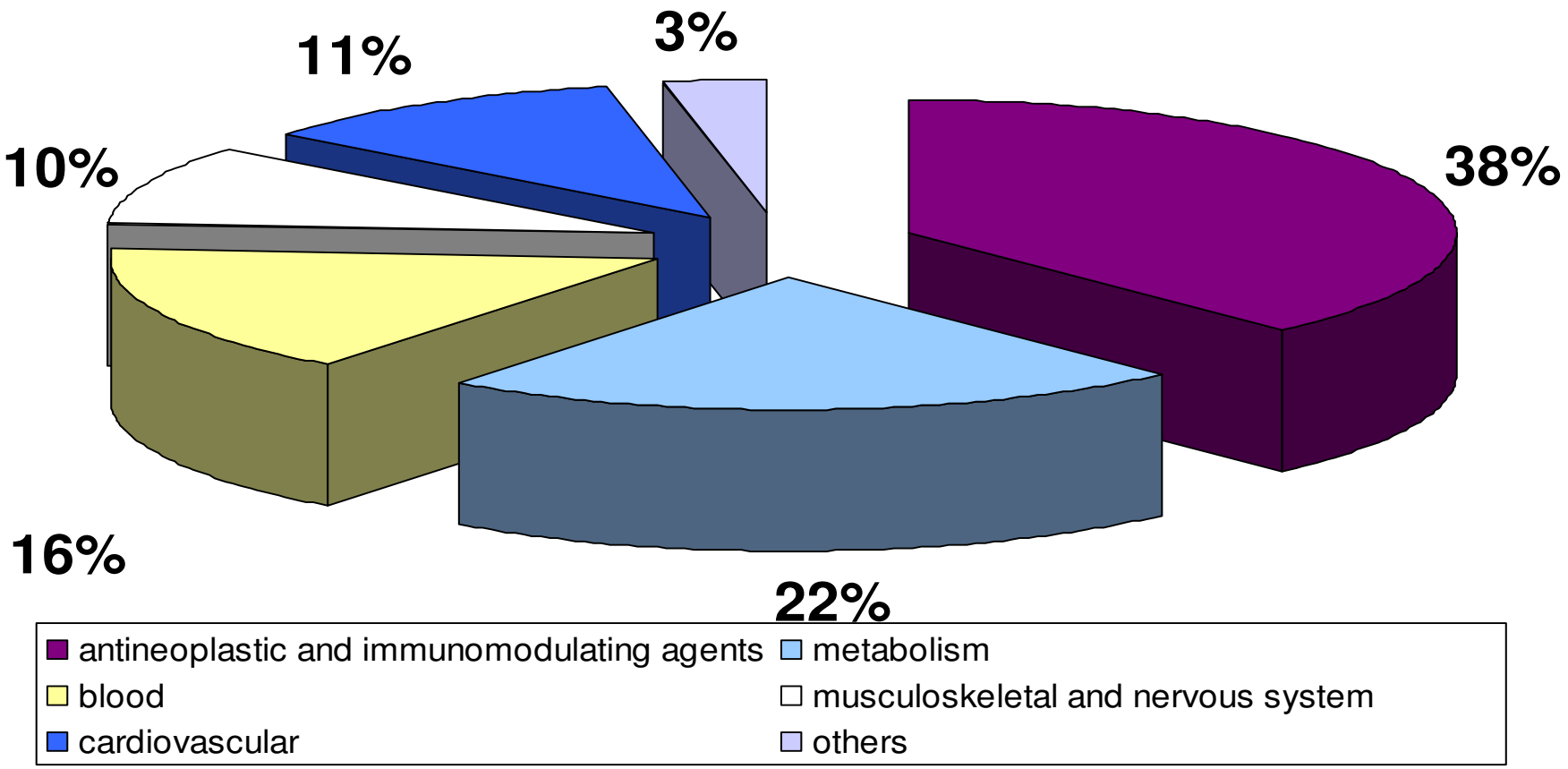
- **63 Marketing Authorisations**

- **Adopted positive opinion**
  - TOBI Podhaler for Pseudomonas aeruginosa lung infection in cystic fibrosis
- **Ongoing applications in review process**
  - 16 centralised applications in review process
- **Variations / Line Extensions in review process**
  - 5 applications with variations/line extensions

- **Negative outcomes for orphan MAA**
  - 40 applications for MA withdrawn
  - 6 negative decisions/refusals

Distribution of Orphan MAA

62 orphan authorised by centralised MA*



*2 withdrawn from the register of orphan drugs

For more information…

- 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, 9July 2007 (ENTR/6283/00 Rev 3)

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

Guidance Documents (cont.)

- Points to consider on the calculation and reporting of the prevalence of a condition for orphan designation (EMEA/COMP/436/01)
- Guideline on clinical trials in small populations (CHMP/EWP/83561/2005)