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Use of core outcome sets in EMA guidelines

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COMET IV
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In this talk...

- Criteria for Marketing Authorisation
- Outcome Measures - Regulatory Requirements
- EMA Guidelines – COS examples
- EMA Scientific advice qualification process
- Conclusion

Disclaimer

Views expressed are personal, not to be understood or quoted as being made on behalf of the European Medicines Agency or its scientific Committees

What are the criteria for authorising a medicinal product in Europe?

Criteria for Marketing Authorisation (MA)

EU pharmaceutical law

- To demonstrate the quality, safety and efficacy
- Based on objective criteria
- Balance of benefits and risks should be positive

Outcome Measures - Regulatory Requirements

- precisely specified in advance, standardised
- address the primary objective
- ascertainable in all patients
- unbiased (“fair” to each study arm)
- sensitive to meaningful changes in patient's health
- reflect relevant clinical patient benefit
- quantifiable, reproducible
- safe

ICH Guideline E9 Statistical principles for clinical trials

How to improve regulatory acceptance ?

- To consult relevant EMA guidelines

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    - Blood products
    - Cardiovascular system

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Clinical efficacy and safety guidelines

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This section includes the European Medicines Agency's guidelines on the **clinical efficacy and safety of medicines**.

The Agency's Committee for Medicinal Products for Human Use (CHMP) prepares **scientific guidelines** in consultation with regulatory authorities in the European Union (EU) Member States, to help applicants prepare marketing-authorisation applications for human medicines.

Guidelines provide a basis for practical harmonisation of how the EU Member States and the Agency **interpret** and **apply** the detailed requirements for the demonstration of quality, safety and efficacy that are in the **Community directives**.

The Agency strongly encourages applicants and marketing-authorisation holders to follow these guidelines. Applicants need to justify **deviations from guidelines** fully in their applications at the time of submission. The Agency advises applicants to discuss any proposed deviations with EU regulators during medicine development through scientific advice.

Clinical efficacy and **safety guidelines** are provided for:

- Clinical pharmacology and pharmacokinetics
- Alimentary tract and metabolism
- Blood and blood forming organs
- Blood products (including biotechnological alternatives)
- Cardiovascular system
- Dermatologicals
- Genito-urinary system and sex hormones
- Anti-infectives for systemic use
- Antineoplastic and immunomodulating agents
- Rheumatology/Musculo-skeletal system
- Nervous system
- Respiratory system
- General
- Herbal medicinal products
- Information on medicinal products

Development of EMA guidelines

- Formalised process
- GL drafting group to prepare draft document

Operational structure of EMA

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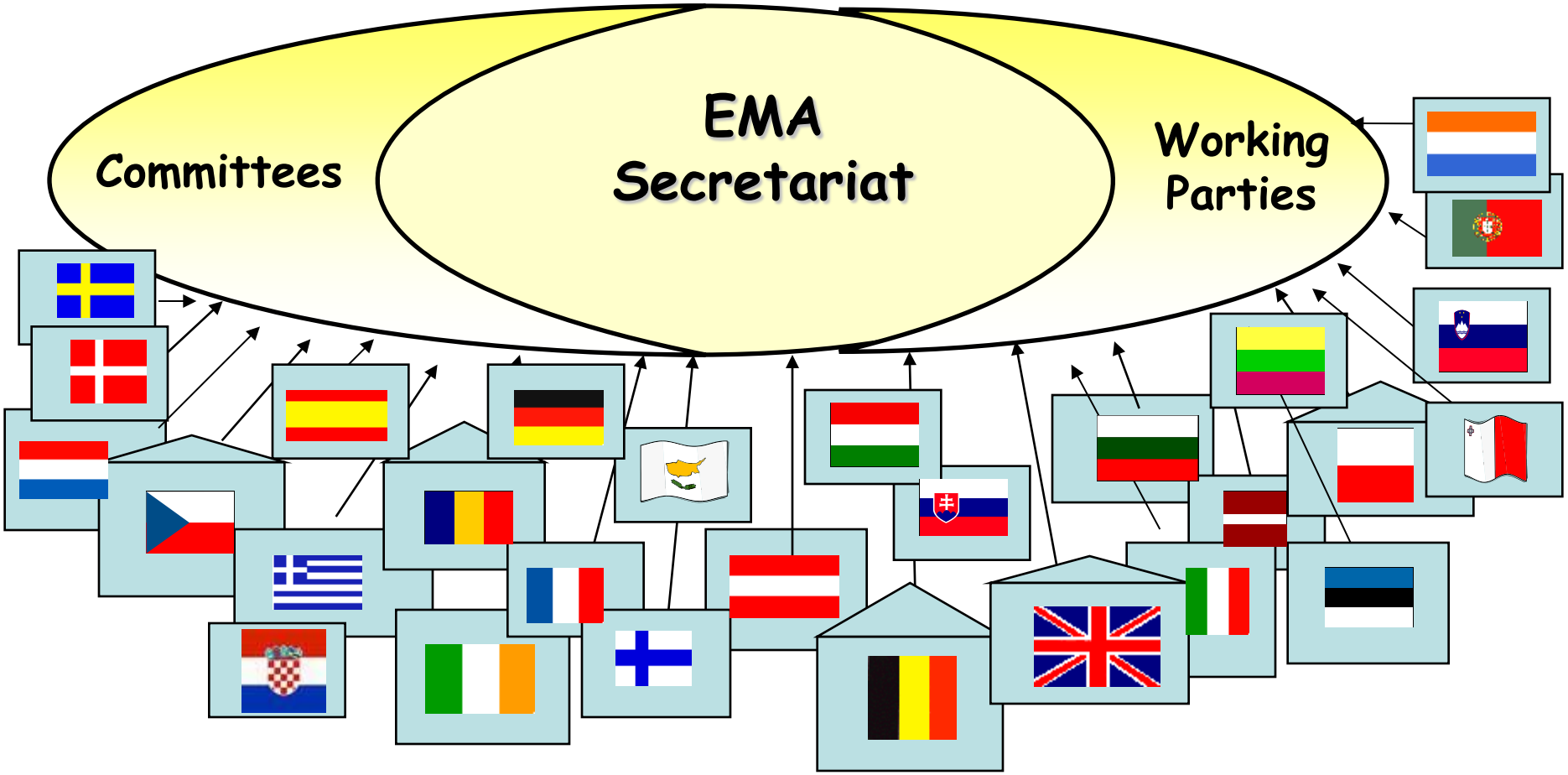
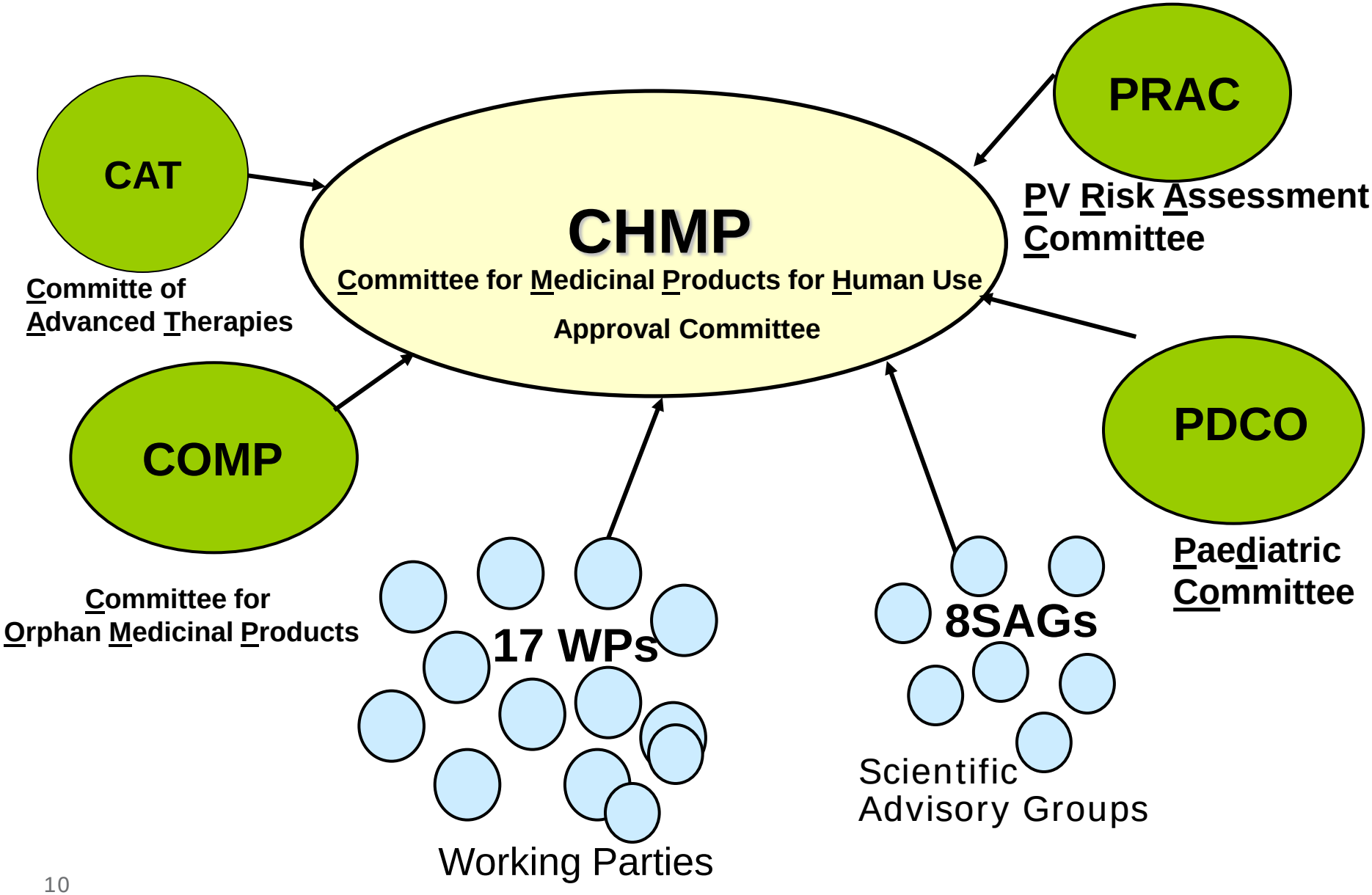
EMA and the European Regulatory Network



Operational structure of EMA



Development of EMA guidelines

- Formalised process
- GL drafting group to prepare draft document
- Discussed with committees
- Put for public consultation

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Specific privacy statement for public consultations

30/10/2014

Draft guideline on influenza vaccines – submission and procedural requirements

27/10/2014

Guidance on the assessment of persistent, bioaccumulative and toxic or very persistent and very bioaccumulative substances in veterinary medicine

15/10/2014

Concept paper on the need for revision of the points to consider on the clinical investigation of new medicinal products for the treatment of acute coronary syndrome

14/10/2014

EMA scientific guidelines - how to develop a medicinal product

- Define outcome measures which should be used as endpoints in clinical trials
- Outcome measures based on
  - current available published evidence
  - obtained through expert meetings

EMA guidelines and COS

- Frequently clinical trial sponsors select outcome measure in isolation ⇒ impossible to compare results with those of other studies
- **COS** allow comparison / synthesis of clinical trials
- Indirect comparison for relative efficacy / comparative effectiveness

Example 1 - Juvenile idiopathic arthritis

- Draft **GL** on clinical investigation of medicinal products for treatment of **juvenile idiopathic arthritis**
- End of public consultation: 15 November 2014
- Recommended primary endpoint for parallel randomised trials:

  Change in ACR paediatric core set criteria

ACR Paediatric JIA core set

- number of active joints
- number of joints with limited range of motion
- physician's global assessment
- patient/parent's global assessment
- functional ability
- laboratory marker of inflammation

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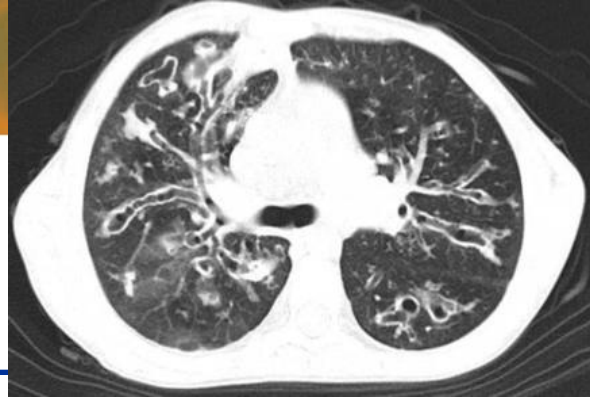
25 April 2014
EMA/CHMP/239770/2014 Rev. 2
Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis
Draft

Draft agreed by Rheumatology Immunology Working Party and PDCO	April 2014
Adoption by CHMP for release for consultation	25 April 2014
Start of public consultation	15 May 2014
End of consultation (deadline for comments)	15 November 2014

The proposed guideline will replace the guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (CPMP/EWP/422/04)

Example 2: EMA Guideline on CF



Pulmonary disease efficacy data

- Clinical endpoint : assessment of respiratory function
- FEV1: recommended primary endpoint

BUT

- Disease modifying drugs ideally to be administered before lung damage
- FEV1 not optimal for evaluating novel therapies aimed at earliest stages of CF lung disease

→ new measures of early lung damage are needed

List of core outcomes from which to choose primary outcomes

- Lung function: FEV1; in early disease FEF 25-75, LCI
- Pulmonary exacerbations / need for additional antibiotic therapy/ hospitalisation
- validated PRO measures
- Imaging: chest CT score for bronchiectasis/air trapping
- Biometry: weight; in children also height
- Biomarkers depending on the drug class and the supposed mechanism of action

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/12/WC500136159.pdf

Example 3 – Ulcerative colitis

- Lack of scientific consensus on efficacy endpoints/disease outcome assessments
- Hurdle for global drug development in paed UC
- i-IBD working Group: EMA, FDA, Health Canada, PMDA (Japan)
- Many disease activity indices developed, but responsiveness, reliability, validity not properly validated
- **Consensus on efficacy endpoints and disease activity indices needed for globalization of paediatric UC trials**

J Pediatr Gastroenterol Nutr 2014

Example 4 - Osteoporosis

- How to measure clinically relevant benefit in CTs in children with osteoporosis
- Paediatic osteoporosis expert meeting at EMA June 2014
- Primary outcome measure: frequency of fractures

BUT

- Fractures rare in children
- Bone mineral density limited value in predicting fractures
- Development of composite endpoint including number of fractures, bone mineral density and other parameters (quality of life including functioning, laboratory markers) warranted

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/09/WC500172407.pdf

EMA qualification process - Novel Methodologies

- Voluntary scientific pathway
- Scientific Advice on future protocols and methods for further method development towards qualification

  e.g. *can this novel methodology be used as inclusion criterion or as an endpoint in a clinical trial*?
- Qualification Opinion on the acceptability of a specific use of the proposed method

Conclusion

- EMA interested in development and availability of COS
- Need to validate and standardize COS:
  - objective, true predictor of clinical benefit, sensitive to changes
- EMA qualification process: unique opportunity for early discussion of trial design and endpoints with regulators
- Need to increase early interaction between regulators and stakeholders on requirements for marketing authorisation

Thank you

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