Neuroprotection & PD

European Regulatory Perspective On The Concept Of Disease Modification In Parkinson's Disease

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Role of EMEA

- Centralized authorization of medicinal products for human use in Europe
  - **Mandatory for (EU Regulation 726/2004 – enforced Nov 2005)**
    - **new active substance**
    - **Indication: neurodegenerative disorder**
- Committee for Medicinal Products for Human Use (CHMP)
  - **Scientific Advice Working Party (SAWP)**
    - **Internal and external experts**
    - **Scientific advice but no regulatory compromise**

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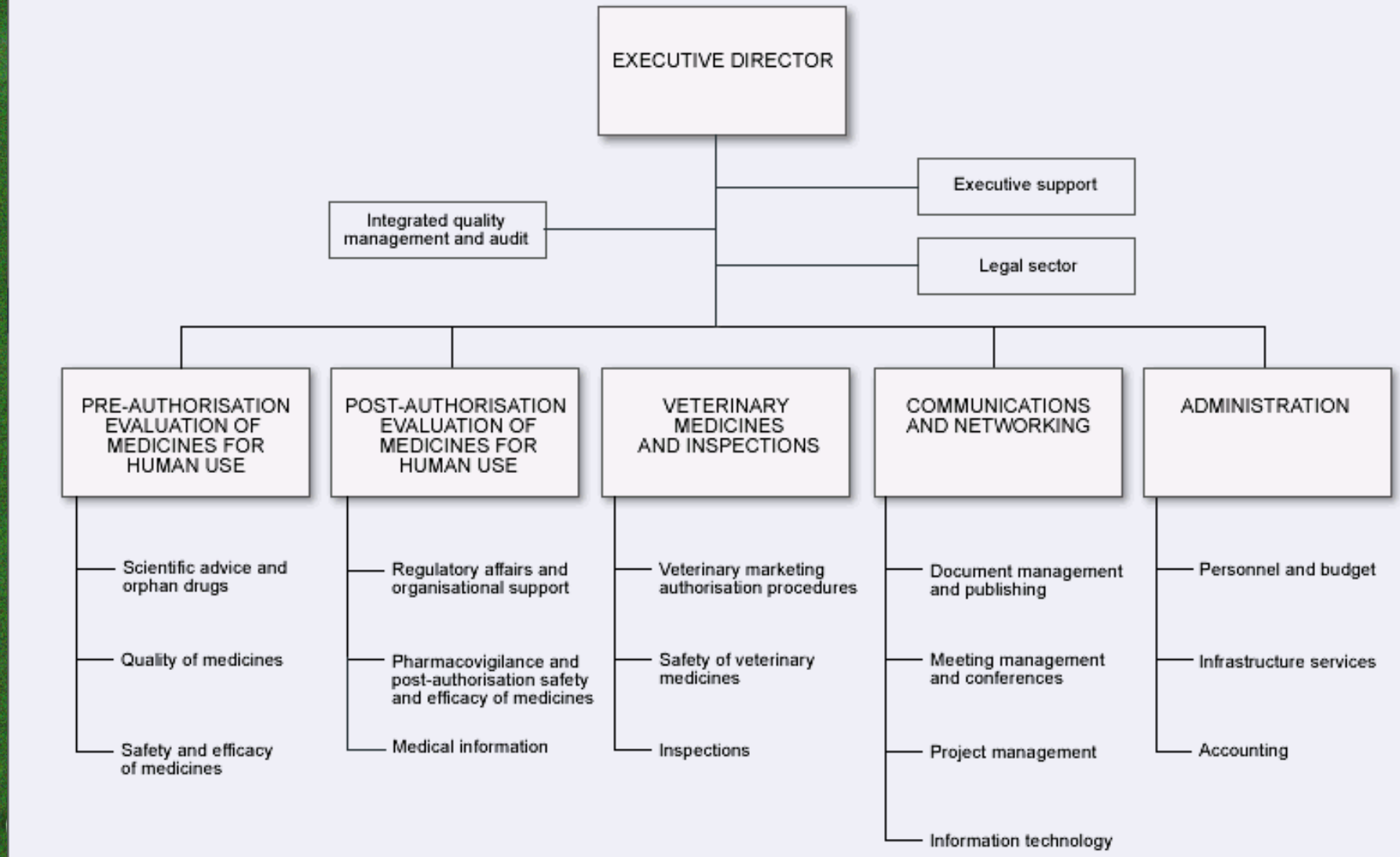
Role of EMEA


EXECUTIVE DIRECTOR
Executive support
Integrated quality management and audit
Legal sector
PRE-AUTHORISATION EVALUATION OF MEDICINES FOR HUMAN USE
POST-AUTHORISATION EVALUATION OF MEDICINES FOR HUMAN USE
VETERINARY MEDICINES AND INSPECTIONS
COMMUNICATIONS AND NETWORKING
ADMINISTRATION
Scientific advice and orphan drugs
Quality of medicines
Safety and efficacy of medicines
Regulatory affairs and organisational support
Pharmacovigilance and post-authorisation safety and efficacy of medicines
Medical information
Veterinary marketing authorisation procedures
Safety of veterinary medicines
Inspections
Document management and publishing
Meeting management and conferences
Project management
Information technology
Personnel and budget
Infrastructure services
Accounting

EMEA Official Statements

Note for guidance on clinical investigation of medicinal products in the treatment of Parkinson's Disease (Committee for Proprietary Medicinal Products [CPMP], June 1999

PD Study Objectives

1. Symptomatic relief in early-stage PD before LD Rx
2. Symptomatic relief in patients with PD on LD Rx:
   - Patients on LD with insufficient control of motor symptoms
   - Patients on LD with dose dependent motor fluctuations
   - Patients on LD with non-dose dependent motor fluctuations
3. Therapies aimed to reduce disease progression
   - Aimed to postpone late non-dose related motor fluctuations
   - Neuroprotective therapies

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EMEA Official Statements

Note for guidance on clinical investigation of medicinal products in the treatment of Parkinson's Disease (Committee for Proprietary Medicinal Products [CPMP], June 1999

- Therapies aimed to reduce disease progression
  - **Aimed to postpone late non-dose related motor fluctuations**
    - **Long term, double-blind, placebo-controlled add-on studies**
    - **Primary: time to late motor complications (not recommended reduction LD)**
    - **Durations: yrs**
    - **New study designs justified**
  - **Neuroprotective therapies**
    - **Long term, double-blind, placebo-controlled add-on studies (± LD)**
    - **New designs accepted but justified**
    - **Washout accepted**
    - **Neuroimaging advocated but early to accept as primary endpoint**

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EMEA/Europe Uncompromising Statements

- Slowing the Progression of Neurodegenerative Diseases: Medicinal Products Clinical Development - EMEA/CHMP/EWP Workshop, October 2006

- Disease-modifying trials in Alzheimer's disease: a European task force consensus (European Alzheimer's disease Consortium), January 2007 (Lancet Neurology)

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EMEA Uncompromising Statements

- Disease-modifying trials in Alzheimer's disease: a European task force consensus (European Alzheimer's disease Consortium), January 2007 (Lancet Neurology)

- **Recommendations for disease-modifying trials**

Target population
- Early Alzheimer's disease
- Mild to moderate Alzheimer's disease

Study design
- Randomised, parallel, two-arm, placebo-controlled trial

Follow-up
- 18 months

Statistical analysis proposed
- Slope analysis

Primary and secondary outcomes
- Endpoints should be clinically relevant and include cognitive functions (composite measures), functional status (activities of daily living), neuropsychiatric symptoms (NPI) and cost-effectiveness (RUD, Zarit)
- Biomarkers (biological and neuroimaging)

Surrogate markers
- Not recommended for primary outcome at this time

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Concept of Disease-Modifying Treatments

- Reduce progression rate
- Long lasting effect on disability in opposition to impairment (clinical signs and/or symptoms)
  - Accepted a DME + symptomatic improvement
- Postponing disability and dependence (hard outcomes)
- Consequentiality approach (sound clinical outcomes) in detriment of a mechanistic (pathophysiological process)

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Trial Design - Population

- Population to be studied
  - Early stages but with well accepted clinical diagnostic criteria
    - Pre-symptomatic PD but with parkinsonism
    - Not exclusive genetic or imaging diagnosis
  - Moderate PD
  - Any stage with “rapid” disease progression
    - Not late stages
- Population arbitrarily divided into:
  - At risk – pre-morbid status
    - Experimental
    - No therapeutic need
    - Not eligible for non proof of concept trials
  - Early
    - eligible
  - Advanced disease
    - eligible

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Trial Design

- Parallel RCT
  - Favored
  - Compare progression rates if predefined a clinically relevant difference
  - Time to event comparison
    - Event: clinical significant milestone
    - Delay clinical relevant milestones: AD 6 months; PD 1 yr
  - Duration:
    - > = 18 months AD (4 points AD cog yr)
    - PD > 2-3 yrs (?)
- Randomized start/withdrawal
  - Mechanistic approach
  - Duration per period (>12 months)
- Adaptive trials
  - Reduction sample-size
  - Reduction duration of follow-up
  - Advocated
- Sequential design !

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Trial Design - Endpoints

- Early untreated
  - Change in UPDRS
  - Time to LD/DA (problematic)
  - 9-24 months
- Stable treated
  - Emergence of clinical relevant milestones
    - axial symptoms
      - » freezing of gait
      - » loss of balance
      - » H&Y III
  - 2-5 yrs
- Advanced PD
  - Prevention of disability
    - » Autonomic failures
    - » Falls
    - » Cognitive symptoms
    - » Time to "dementia"
    - » Time to nursing home placement
  - > 5 yrs

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Trial Design - Analysis

- **Problems:**
  - **≠ study progression rates at different disease stages**
  - **Missing data / ITT / imputation techniques**

– **Early disease – known slope:**
  - **Slope analysis**

– **Advanced disease:**
  - **Time to a milestone (survival analysis)**

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Role of Surrogate Endpoints/Biomarkers

- Fixed biomarkers - population selection
  - Candidates
    - genetic
    - neuroimaging
- Dynamic biomarkers – surrogate outcomes
  - No accepted correlation with primary clinical endpoints

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Role of Surrogate Endpoints/Biomarkers

- Incentivation to pursue study of biomarkers
  - Recognition of a need
  - Useful for at risk non-benefit population
  - Dose-finding definition
  - Suggestion to collect neuroimaging data as secondary outcome to pursue surrogate endpoint characterization

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Therapeutic Indication Label

- How to call a long lasting beneficial effect?
- Narrative indication!

- **EMEA**
  - **–"Riluzole is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS)."**
- **FDA**
  - **–"RILUTEK is indicated for the treatment of patients with amyotrophic lateral sclerosis (ALS). Riluzole extends survival and/or time to tracheostomy."**

- **Note for guidance on SPC "therapeutic indications"**
  - **–"Study endpoints should not normally be included …"**
  - **–No mechanistic indication**
    - **X neuroprotection**

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General Considerations

- Parallel design favored
- Favored time to clinical relevant endpoints
- Accepted comparative rates of progression (slope analysis) if predefined a clinically relevant difference
- Withdrawal designs problematic due to unknown duration of washout
- Doubts regarding the Wash-in /wash-out design to demonstrate DM (more data needed)
- Need for long term follow-ups
- Stimulation for incorporation of potential biomarkers as secondary endpoints
- Proof of concept ≠ long term phase III

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European Specificities

- Labelling – centralized
- Price
- Reimbursement

national level

Need for hard clinically relevant outcomes

- Marketing authorization ≠ commercialization

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