Dementia from a Regulatory Perspective
Challenges, Opportunities, Requirements

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EMA committees

SAWP

CHMP
(Committee for Human Medicinal Products)
Chair: Dr. E. Abadie – Vice Chair: Dr. T. Salmonson

COMP
(Committee for Orphan Medicinal Products)
Chair: Dr. K. Westermark – Vice Chair: Mrs. B. Byskov Holm

HMPC
(Committee for Herbal Medicinal Products)
Chair: Dr. K. Keller - Vice-Chair: Dr. I. Chinou

PDCO
(Paediatric Committee)
Chair: Dr. D. Brasseur - Vice-Chair: Dr. G. Pons

CAT
(Committee for Advanced Therapy Medicinal Products)
Chair: Dr. C. Schneider - Vice-Chair: Prof. P. Salmikangas
CHMP centralised evaluation

(Co)Rapporteurs’ Assessment Report
Day 80

Stop
Clock
Primary Evaluation Phase

Max. 6 m

Start
Clock
Secondary Evaluation Phase

Day 1

Biotech MPs
- recombinant DNA
- controlled gene expression
- mAbs

Orphan MPs

Therapeutic areas
- Oncology
- Neurodegenerative disorders
- Diabetes
- Autoimmune and immune disorders
- Viral diseases, HIV/AIDS

ATMPs Reg 1394/2007

Scientific Advice Working Party

standing WP of the CHMP

- only WP specifically addressed in the legislation, Regulation EC 726/2004
- thorough peer-review from CHMP members, ad hoc CHMP discussions of difficult issues
- final advice letter signed by CHMP chair

multidisciplinary expert group

- 28 members put together by expertise, not by Member State, selected based on complementary scientific competence
- 3 COMP, 1 CAT
- 16 are from NCAs, and 12 from academic centers
- SA Section of the EMA secretariat support: 10 medical doctors and pharmacists and 7 secretaries and administrative assistants
- network external experts

  - involvement: average 7/procedure, mainly background academia & regulatory agencies
  - nomination and conflict of interest declaration

protocol assistance for orphan drugs for rare diseases, the SAWP secretariat contacts the Patients' and Consumers' Working Party (PCWP)
Other SAWP activities

Product-related

- SA-PA
- Follow-up advices
- Presubmission meetings & DM

Qualification of Novel Methodologies (BMs) and CHMP Opinion

Workshops EFPIA-SAWP

- 2005 & 2006 Biomarkers
- 2007 Adaptive designs
- 2008 Modeling and Simulation in Paediatric Drug Development
- 2008 Pharmacogenomics
- 2010 Alzheimer’s disease

- PROs, manufacturing, etc.
Scientific Advice and Protocol Assistance

2009: Scientific Advice 311, Protocol Assistance 77
2008: Scientific Advice 264, Protocol Assistance 56
2007: Scientific Advice 215, Protocol Assistance 73
2006: Scientific Advice 201, Protocol Assistance 58
2005: Scientific Advice 136, Protocol Assistance 55
2004: Scientific Advice 87, Protocol Assistance 22
2003: Scientific Advice 72, Protocol Assistance 25
2002: Scientific Advice 71, Protocol Assistance 17
2001: Scientific Advice 69
2000: Scientific Advice 58

* Protocol Assistance = Scientific Advice for Orphan Medicinal Products
SA requests

Scientific-advice requests by therapeutic area (2008)

- Alimentary/Metabolism: 27%
- CNS: 29%
- Antineoplastic: 12%
- Various: 8%
- Antinfectives: 24%
- Blood and blood forming organs: 6.4%
- Dermatologicals: 4.0%
- General anti-infectives for systemic use: 4.0%
- Musculo-skeletal system: 4.0%
- Respiratory system: 4.0%
- Nervous system: 1.8%
- Sensory organs: 1.8%
SAWP areas of expertise

**PRECLINICAL**
- Pharmacology
- Toxicology

**MANUFACTURING/CMC**
- Biotechnology

**THERAPEUTIC AREAS**
- Alzheimer/Biomarkers
- Oncology
- Psychiatry
- Immunology
- Diabetes
- Cardiology
- Endocrinology
- Neurology
- Dermatology
- Clinical Pharm
- Pharmacokinetics
- Ophthalmology
- Clinical Trials/Statistics
Subtypes of Dementia

(Canadian Population)

Trial population:

High specificity of diagnostic criteria more important than high sensitivity!!!
Many new developments are ongoing
Possible Cornerstones in the Treatment of Patients with Dementia

**NfG on Medicinal Products for Treatment of Alzheimer’s Disease**

- **Symptomatic Improvement**
- **Slowing or arrest of progression**
- **Primary prevention**

**NEW: http://www.emea.europa.eu**
Guidance Document

address different types of dementia
differences in severity

- MCI/preclinical/prodromal/very mild
- mild
- moderate
- severe
disease modification
discussion on biomarkers as surrogate endpoints
discussion on adequate study designs
Alzheimer's Disease:

Efficacy (Symptomatic Improvement)

2 primary Endpoints

• mandatory: cognitive domain
  functional domain

• both endpoints should show significant differences

Response criteria for clinical relevance:
proportion of patients with meaningful benefit?

Duration of treatment: at least 6 months

secondary endpoints

• global domain
• additional symptoms
Assessment of overall benefit

Response-Criteria:

- e.g., $\text{ADAS}_{\text{cog}} \geq 4 + \text{Score} \leq 3$ of CIBIC + no change in DAD

Effect size

Numbers Needed to Treat

- (e.g. patients showing improvement of $\text{ADAS}_{\text{cog}} \geq 4$)
Disease modification - Two step approach

“If in a first step delay in the natural course of progression of the disease based on clinical signs and symptoms of the dementing condition can be established, this may be acceptable for a limited claim, e.g. delay of disability. If these results are supported by a convincing package of biological and/or neuroimaging data, e.g. showing delay in the progression of brain atrophy, a full claim for disease modification could be considered.”
Disease Modification

“For regulatory purposes a disease modifying effect will be considered when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes and when this is accompanied by an improvement of clinical signs and symptoms of the dementing condition. Consequently a true disease modifying effect cannot be established solely based on clinical outcome data, such a clinical effect must be accompanied by strong supportive evidence from a biomarker programme”
Design Issues

- study population/add-on populations
- study duration
- which type of endpoints
- type of analysis
  - slope analysis
  - survival analysis
  - randomized start designs/randomized withdrawal
  - missing data/drop outs/LOCF
- valid and reliable scales
Qualification procedure
Qualification of Novel Methodologies

Preclinical development
- pharmacological screening
- mechanism of action
- predict activity/safety
- PK/PD modelling
- toxicogenomics

Clinical development
- verify mechanism
- dose-response
- proof of concept
- input CT design
- surrogate endpoint

Drug utilisation
- optimise target population
- guide treatment regimen
Players in BM development

Multidisciplinary and integrated exercise

- Regulatory Authorities
- Pharma & Biotech Company
- Diagnostic Company
- Academic Investigators
New regulatory procedures

**CHMP Qualification Opinion** on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data, not specific to one product.

**CHMP Qualification Advice on future protocols and methods for further method development towards qualification**, based on the evaluation of the scientific rationale and on preliminary data submitted.

**AIMS**

SAWP/CHMP *early involvement* in the design of the strategy towards qualification of novel methodologies.

SAWP/CHMP *commitment* to evaluate the data obtained from the agreed studies and to provide a Qualification Opinion regarding the use of the method in R&D.

**Goal:** speed up drug development, contribute to public health.
New regulatory procedure

**SCOPE**

Focus on acceptability of specific use of the proposed technology/BM developed for a *specific intended use* in the context of pharmaceutical R&D.

Based on the assessment of submitted data by a specialised BM Qualification team (BMQT), peer review and public consultation.

**Output:** CHMP Qualification Advice and scientific assessment (public document).

**APPLICANTS**

Consortia, Networks, Public/private partnerships, Learned societies, Pharmaceutical industry

**Input:** Protocols, study reports, raw data etc to establish the use of a defined biomarker for a specific purpose in drug development.

**QUALIFICATION OF NOVEL METHODOLOGIES FOR DRUG DEVELOPMENT: GUIDANCE TO APPLICANTS**

Revision of Diagnostic Criteria

Dubois B, Feldman HH, Jucova C et al. 2007

**Core diagnostic Criterion: Early and significant episodic memory impairment**

At least one supportive criterion of

- MTL atrophy shown with MRI
- Abnormal CSF (amyloid-β, tau, phospho-tau)
- Specific pattern shown with PET
- Proven DAT mutation

**Validation studies necessary !!!**
Questions on Surrogate Markers in Dementia

for which clinical outcome the biomarker is used?
does the biomarker reliably predict the clinical outcome?
does the biomarker reflect effects on pathology and/or pathophysiology for a claim of disease modification?
are the effects seen in the biomarkers clinically relevant?
allow results seen short-term generalization to long-term?
Experience to date

• 3 procedures started for Alzheimer, including more than 7 biomarkers
• 2 on going validations
• Currently several sponsors in contact to initiate the procedure
• **C-Path**, Drug Companies
• PET
• Modelling and Simulation
• Amnestic MCI
• Prodromal Alzheimer
• Biomarkers CSF, MRI

• applicants are encouraged to apply in parallel to the EMA and **FDA** (confidentiality agreement), who communicate during the assessment and meet with the Applicant together.
MCI is Prodromal Dementia?

Normal Cognition

Prodromal Dementia

Brain Aging

Mild Cognitive Impairment

Reversible

Stable Or Reversible Impairment

Dementia

Other Dementias

Alzheimer’s Disease

Mixed

Vascular Dementia

Mixed
Clinical Heterogeneity of MCI

**MCI**
- Amnestic
- Single non-memory domain or Multiple domains slightly impaired

**MCI**
- Alzheimer’s disease
  - Normal Aging
  - Alzheimer’s disease
  - Vascular dementia
  - Frontotemporal dementia
  - Lewy body dementia
  - Primary progressive aphasia
  - Parkinson’s disease
Autosomal Dominant Diseases
and the Development of Presymptomatic Treatment Trials
Focus in Alzheimer's and Huntington's Diseases
8th November 2010
New developments in dementia of the Alzheimer’s type
Expert stakeholder meeting
11 January 2010
Protocol Assistance

- Rare Disease (prevalence < 5/10,000)
  - Yes
- Serious or life-threatening?
  - Yes
- Existence of satisfactory methods?
  - Yes
- +Significant Benefit?
  - No
  - Yes

ORPHAN DESIGNATION
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Links

**EMEA guidance for companies requesting SA or PA**


**Qualification of novel methodologies for drug developments**


**Scientific guidelines**

thanks!

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