EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dementia from a Regulatory Perspective
Challenges, Opportunities, Requirements

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European Medicines Agency

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

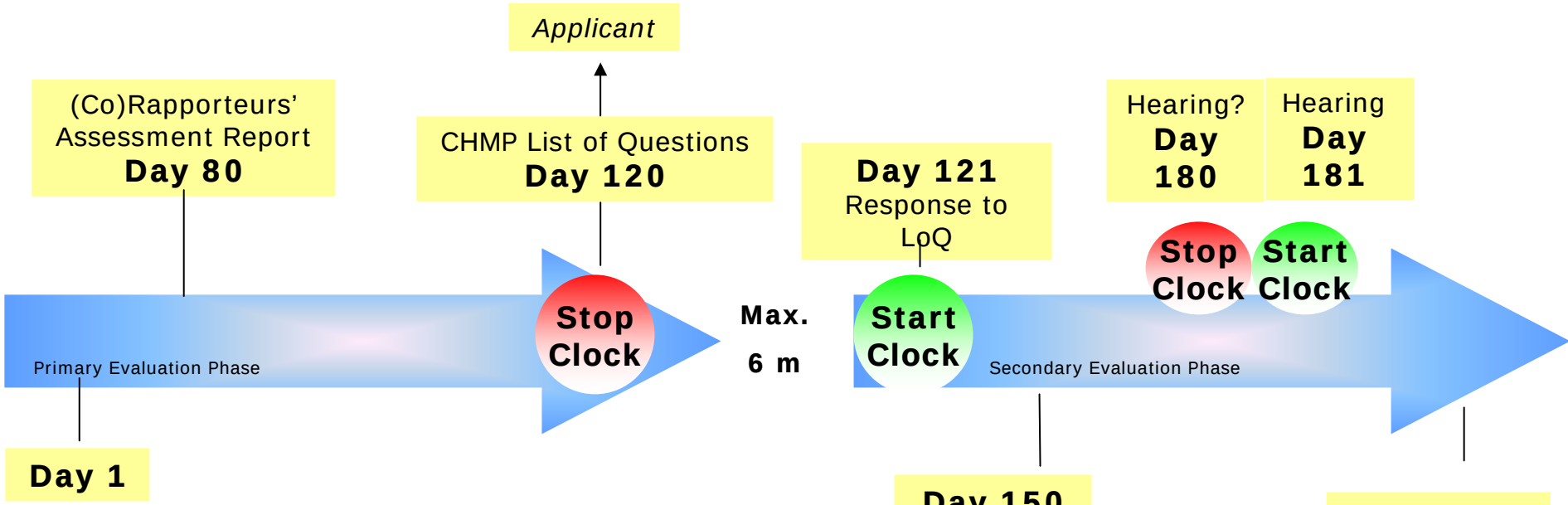
PDCO

(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



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

Regulation (EC) No 726/2004 - Annex I

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

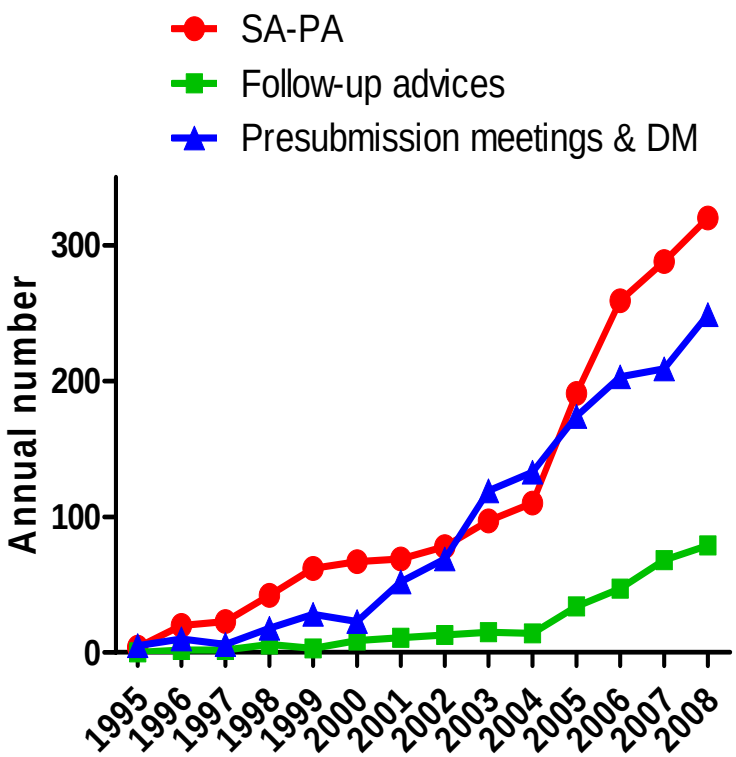
multidisciplinary expert group

- 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



Broad advice

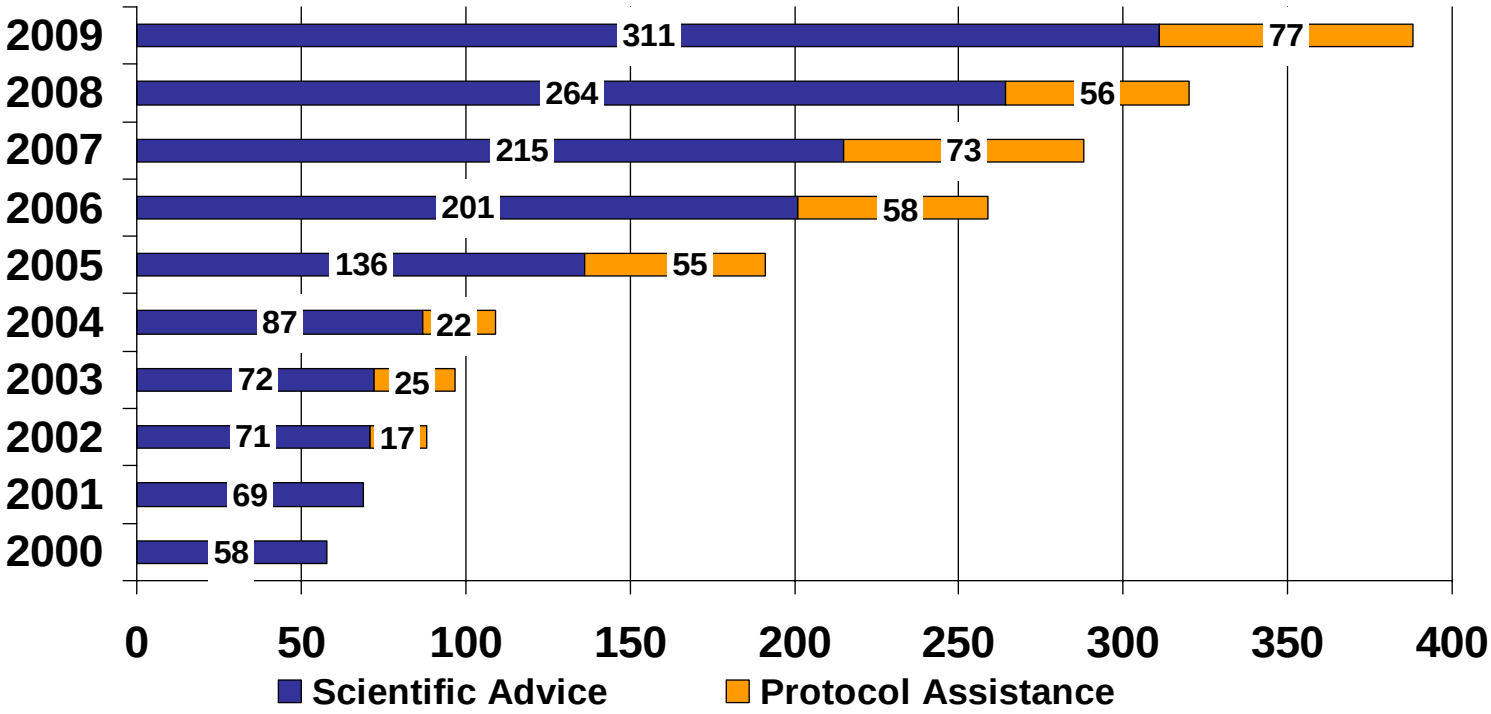
- PROs, manufacturing, etc.

Qualification of Novel Methodologies (BMs) and CHMP Opinion

Workshops EFPIA-SAWP

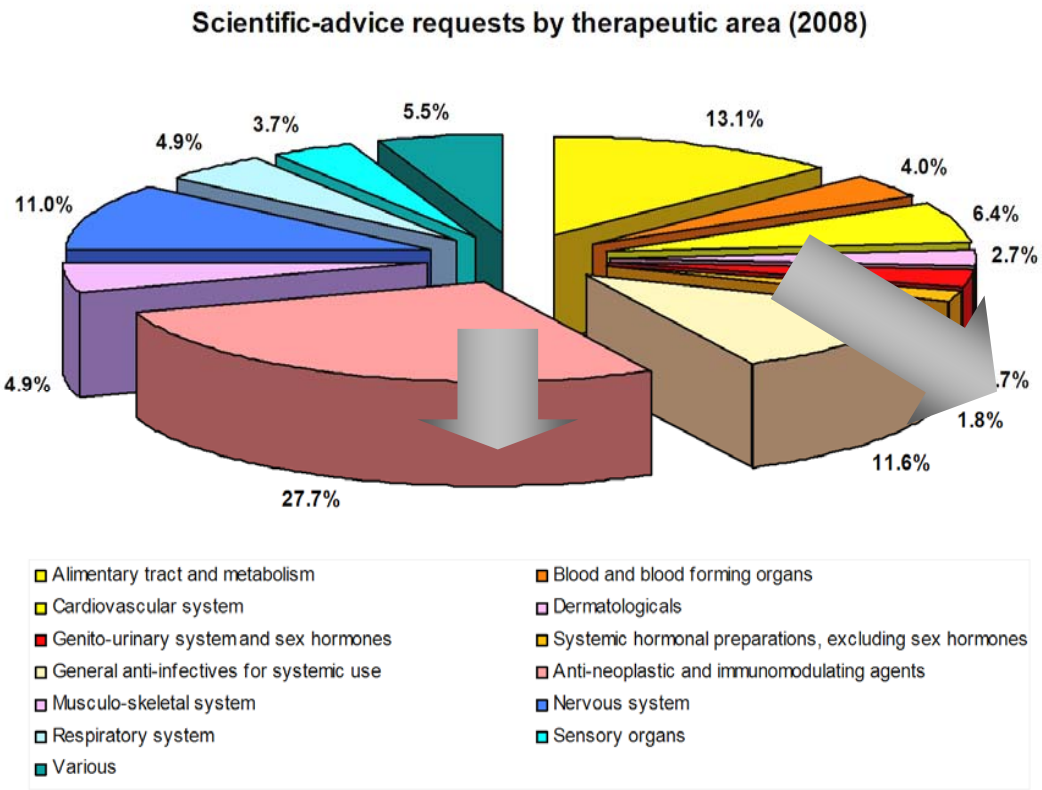
- 2005 & 2006 Biomarkers
- 2007 Adaptive designs
- 2008 Modeling and Simulation in Paediatric Drug Development
- 2008 Pharmacogenomics
- 2010 Alzheimer's disease

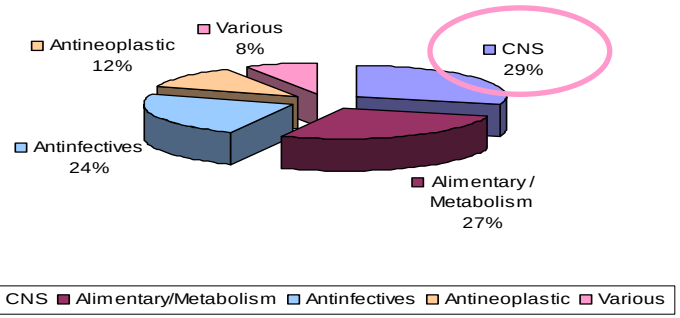
Scientific Advice and Protocol Assistance



* Protocol Assistance = Scientific Advice for Orphan Medicinal Products

SA requests


Scientific-advice requests by therapeutic area (2008)
5.5%
3.7%
4.9%
11.0%
4.9%
27.7%
13.1%
4.0%
6.4%
2.7%
1.8%
11.6%
Alimentary tract and metabolism
Blood and blood forming organs
Cardiovascular system
Dermatologicals
Genito-urinary system and sex hormones
Systemic hormonal preparations, excluding sex hormones
General anti-infectives for systemic use
Anti-neoplastic and immunomodulating agents
Musculo-skeletal system
Nervous system
Respiratory system
Sensory organs
Various


Antineoplastic
12%
Various
8%
CNS
29%
Antinfectives
24%
Alimentary /
Metabolism
27%
CNS
Alimentary/Metabolism
Antinfectives
Antineoplastic
Various

SAWP areas of expertise

PRECLINICAL
Pharmacology
Toxicology

MANUFACTURING/CMC
Biotechnology

Alzheimer/Biomarkers

SA requests to date

THERAPEUTIC AREAS

Psychiatry

Oncology

Immunology

Diabetes
Endocrinology

Cardiology

Neurology

Dermatology

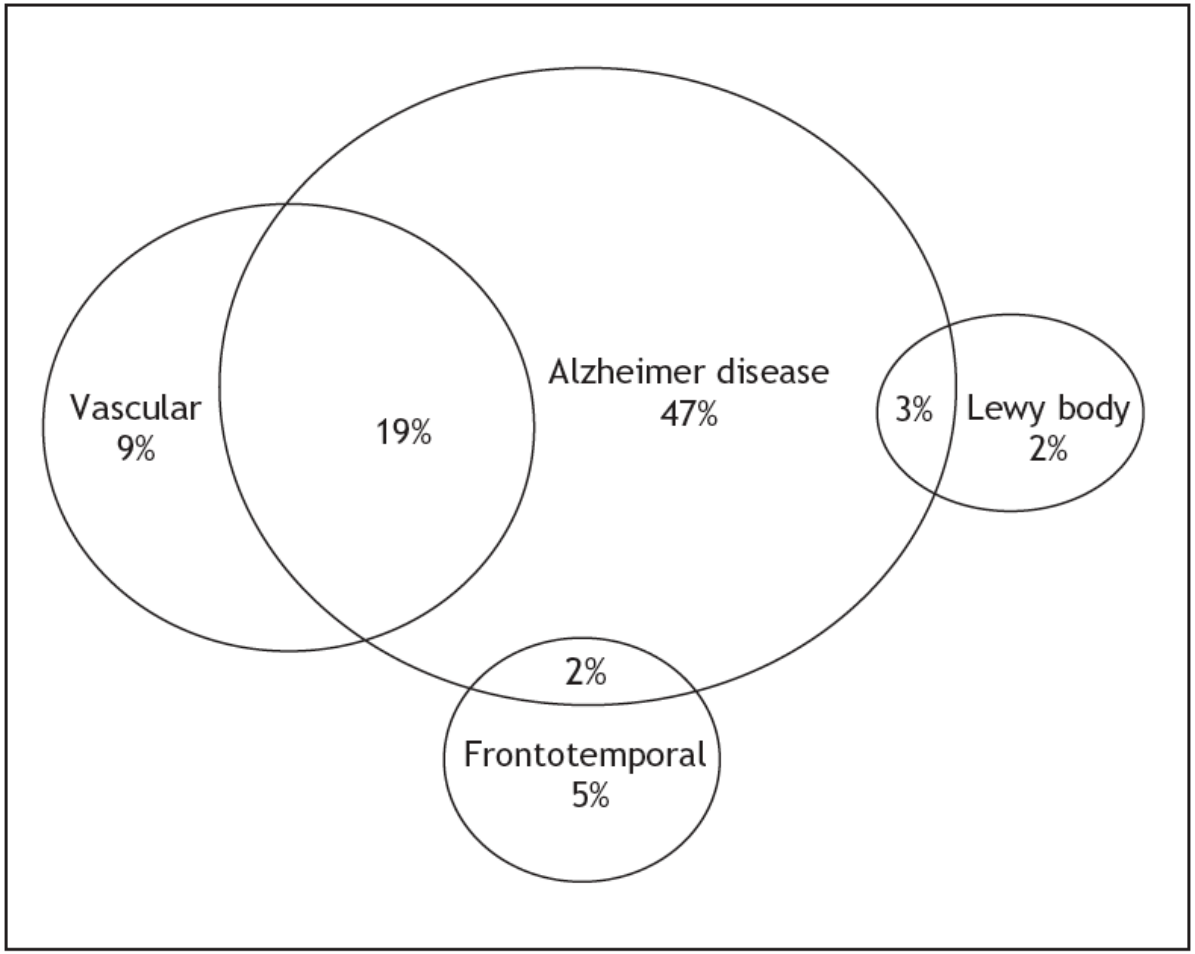
Ophthalmology

Clinical Pharmacology
Pharmacokinetics

METHODOLOGY
Clinical Trials/Statistics

Subtypes of Dementia

(Canadian Population)

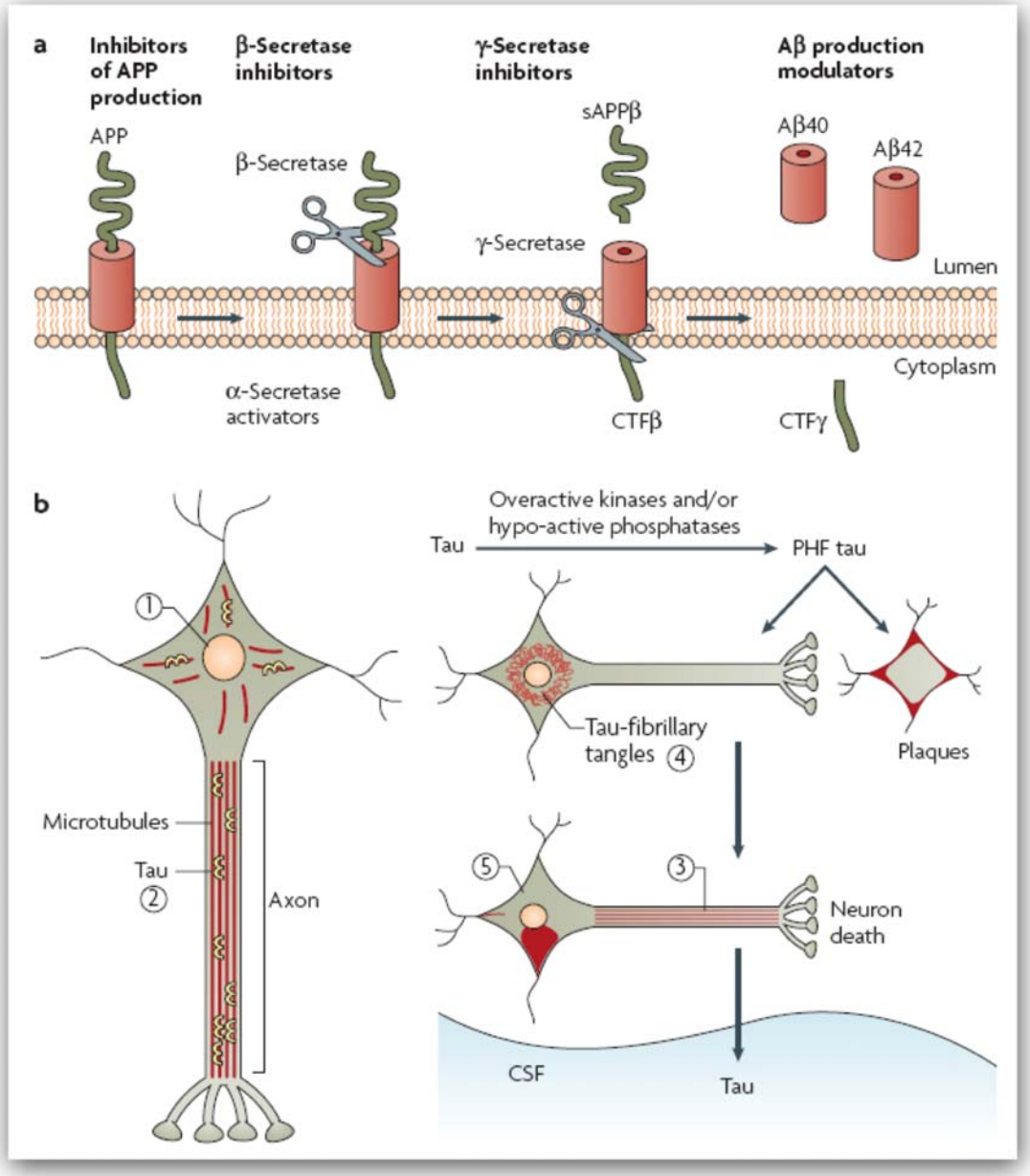


Trial population:

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.. ADAScog ≥ 4 + Score ≤ 3 of CIBIC + no change in DAD

Effect size

Numbers Needed to Treat

(e.g. patients showing improvement of ADAScog ≥ 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

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Qualification procedure

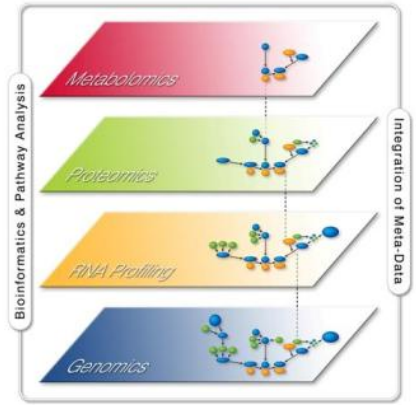
Qualification of Novel Methodologies

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**

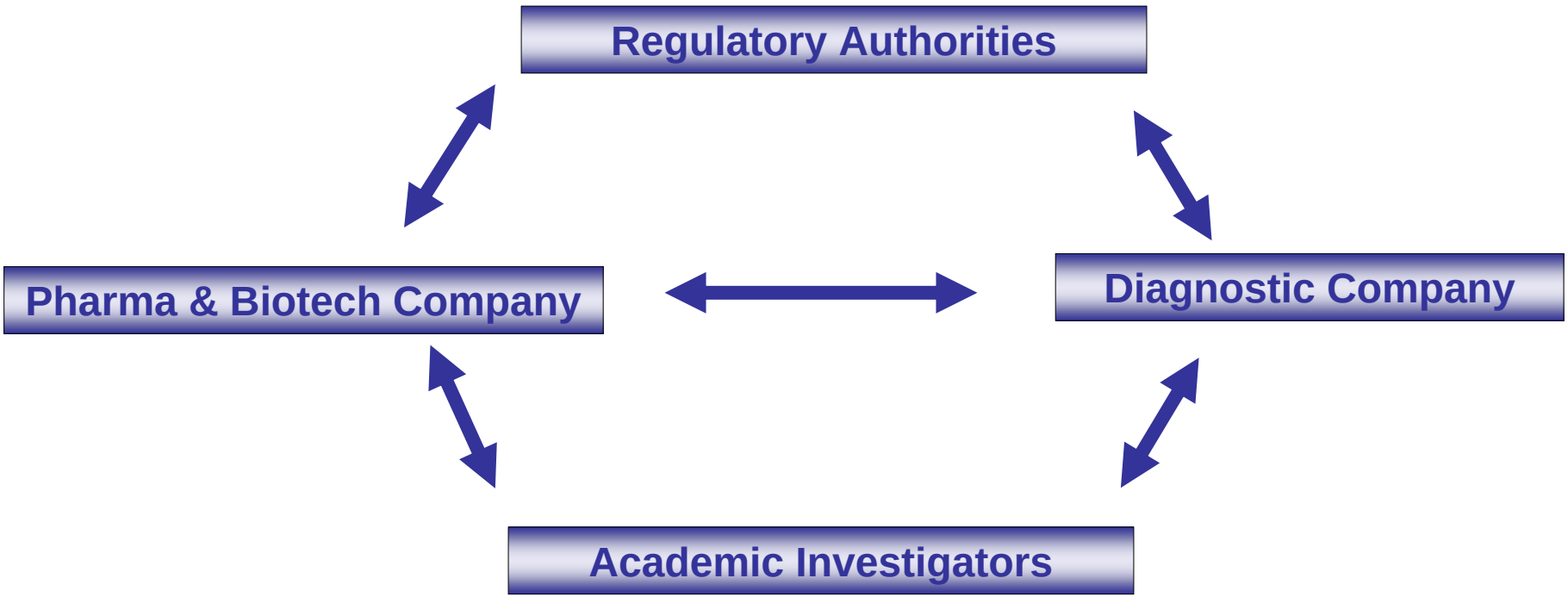


Drug utilisation

- optimise target population
- guide treatment regimen

Players in BM development

Multidisciplinary and integrated exercise



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

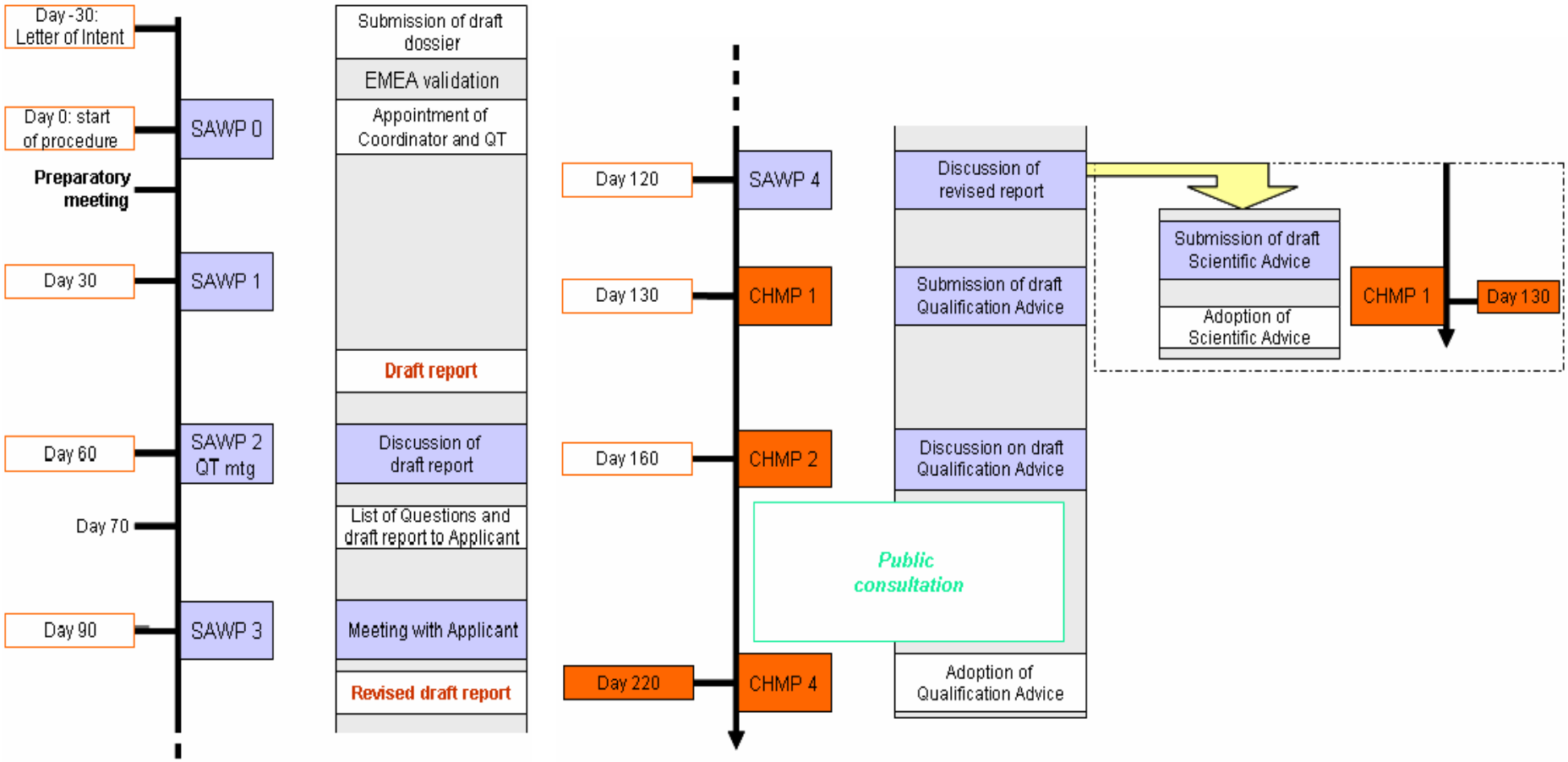
Consortia, Networks, Public/private partnerships, Learned societies, Pharmaceutical industry

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

http://www.emea.europa.eu/pdfs/human/biomarkers/7289408en.pdf

BM Qualification procedure flow



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-ß, 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 ?

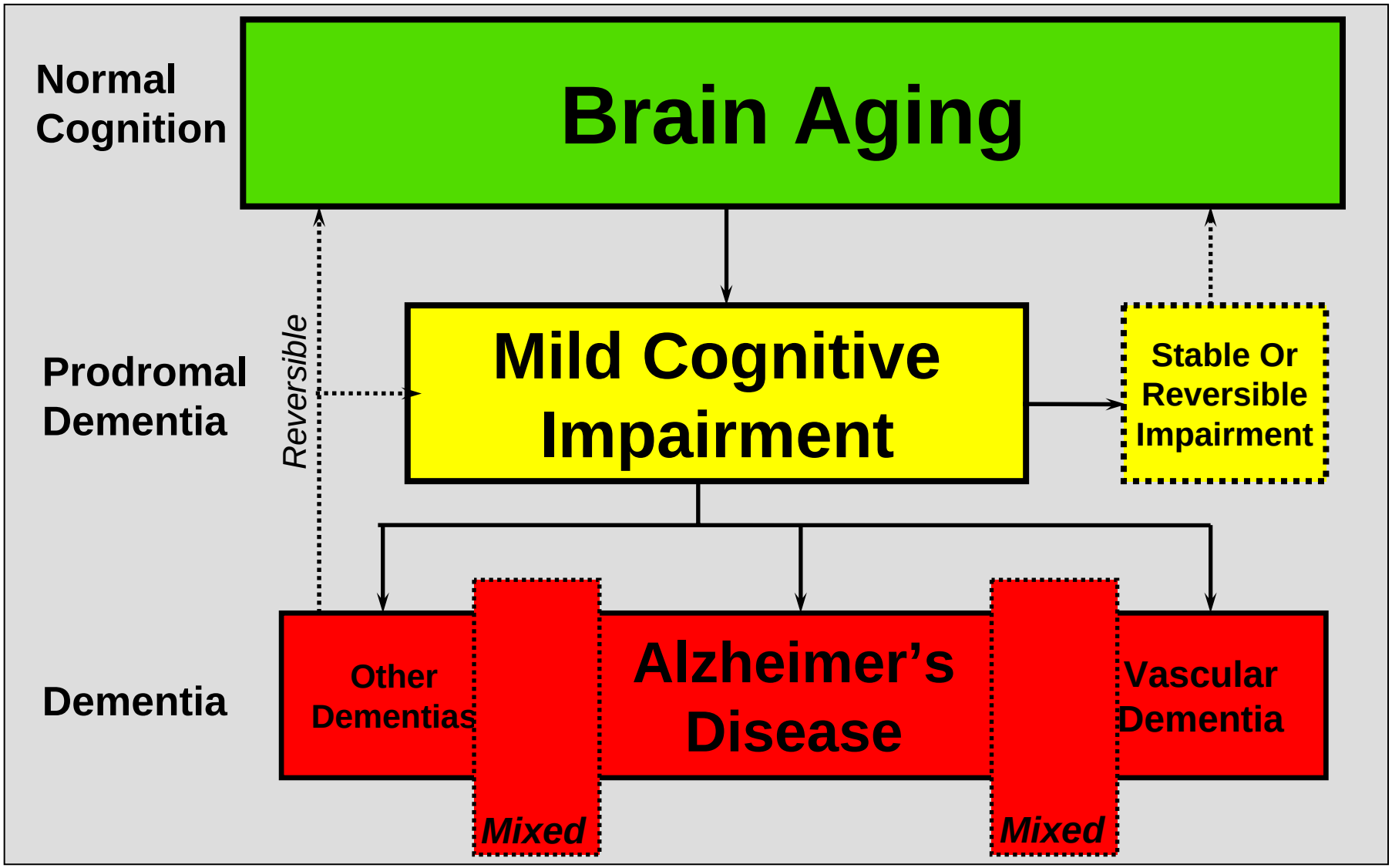
are the effects seen in the biomarkers clinically relevant ?

allow results seen short-term generalization to long-term ?

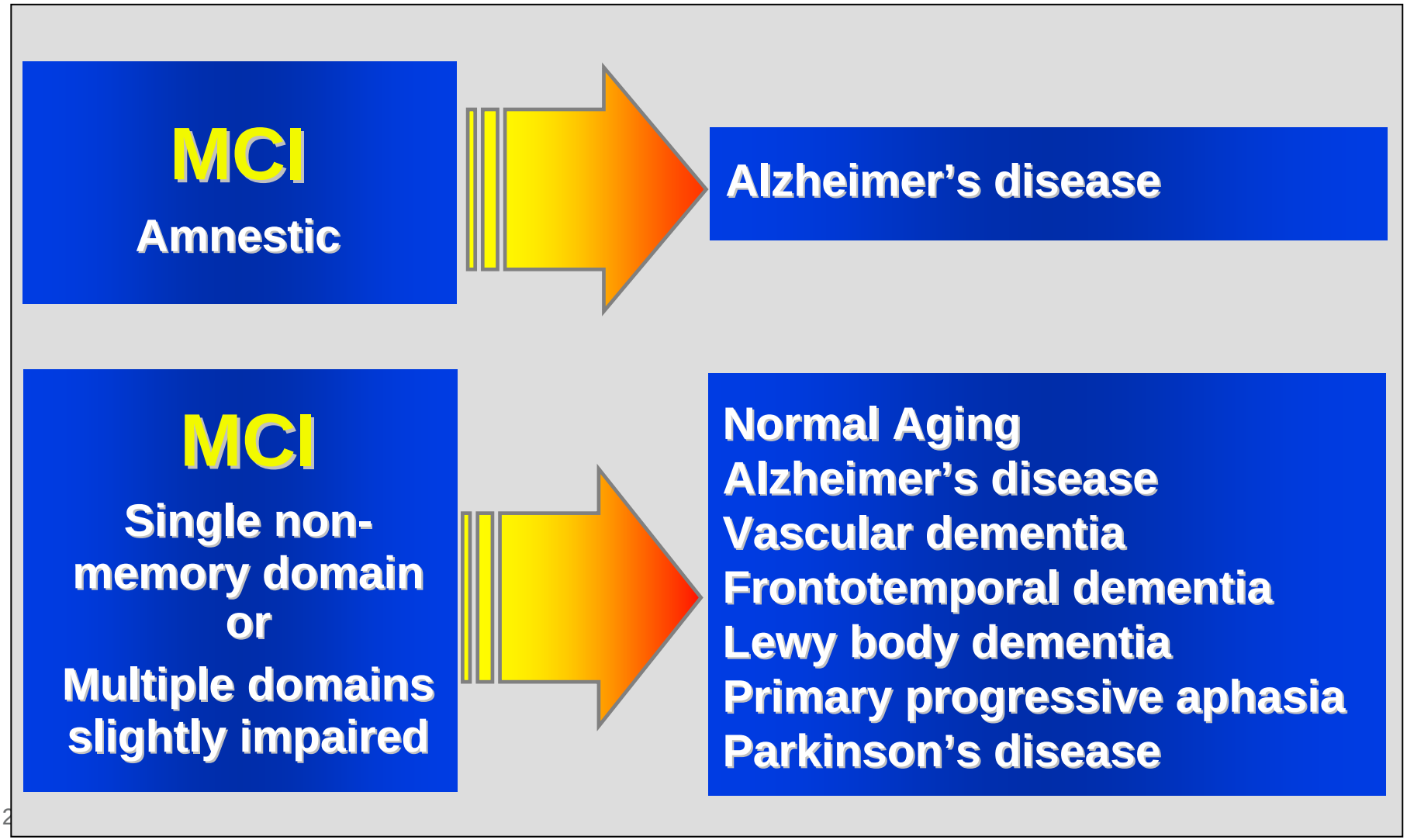
Experience to date

- 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 ?



Clinical Heterogeneity of MCI



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?

+Significant Benefit?

No

Yes

Yes

ORPHAN DESIGNATION

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Links

EMEA guidance for companies requesting SA or PA

http://www.emea.europa.eu/pdfs/human/sciadvice/426001en.pdf

Qualification of novel methodologies for drug developments

http://www.emea.europa.eu/pdfs/human/biomarkers/7289408en.pdf

Scientific guidelines

http://www.emea.europa.eu/htms/human/humanguidelines/background.htm

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