Regulator's view on the scientific and regulatory challenges in new mobility outcomes & PROs

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Agenda

- Current issues in CNS
- History of the Guidance for Multiple Sclerosis
- Workshop Multiple Sclerosis at EMA
- Disability: current assessment tools used in MS
- New mobility outcomes
- Patient reported outcomes
- Fampridine, Ataluren
- Outlook

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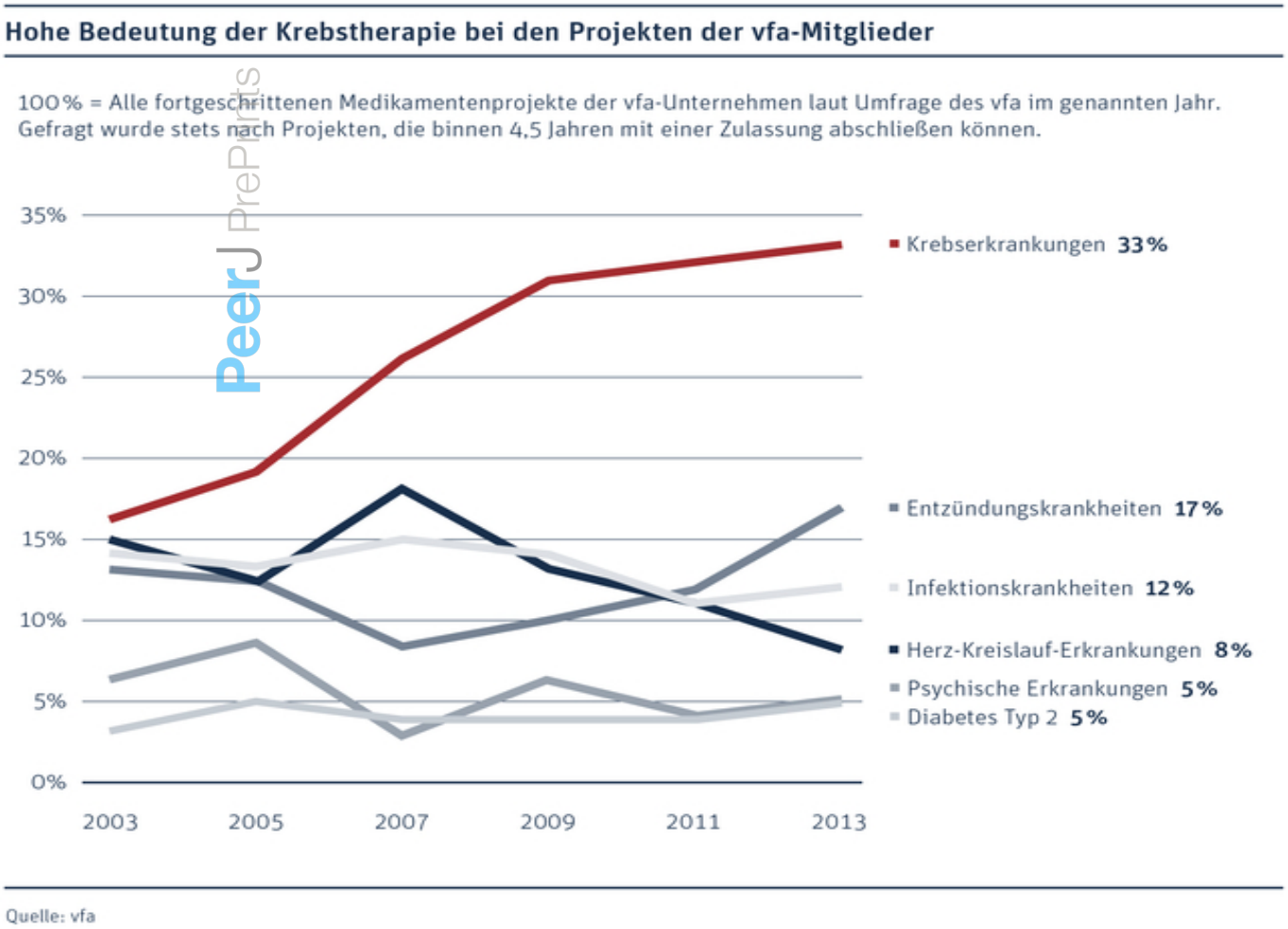
Research Based Pharmaceutical Companies (vfa): Focus on cancer – no focus on CNS



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Many reasons ....

- Problems with preclinical models
- Problems in dose-finding
- Large long-lasting trials
- High failure rate
- .....
- No return of investment

- Regulatory requirements too high ?

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Exception Multiple Sclerosis?

- Fingolimod (2011)
- Fampridine (2011)
- Teriflunomide (2013)
- Alemtuzumab (2013)
- Dimethyl fumarate (2014)

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Hauser SL et al.: Multiple Sclerosis: Prospects and Promise

Ann Neurol (2013) 74: 317-27

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Human medicines
Pre-authorisation
Post-opinion
Post-authorisation
Product information
Scientific advice and protocol assistance
Scientific guidelines
Search guidelines
Quality
Q&A on quality
Biologicals
Non-clinical
Clinical efficacy and safety
Clinical pharmacology and pharmacokinetics
Alimentary tract and metabolism
Blood and blood-forming organs
Blood products
Cardiovascular system
Dermatologicals
Genito-urinary system and sex hormones

Clinical efficacy and safety: Nervous system

This page lists the European Medicines Agency's scientific guidelines on the clinical safety and efficacy of medicines used in nervous-system disorders.

If you have comments on a document which is open for consultation, use the form for submission of comments on scientific guidelines.

Please note that the Efficacy Working Party secretariat e-mail address (ewpsecretariat@ema.europa.eu) no longer exists. Therefore, please submit your comments from now on to the following e-mail address: cnswpsecretariat@ema.europa.eu.

Topic	Documents	Reference number	Publication date	Effective date	Remarks
Need for revision of the guideline on medicinal products for the treatment of Alzheimer's disease and other dementias	Draft concept paper	EMA/CHMP/617734/2013	Released for consultation 31 Oct 2013		Deadline for comments 31 Jan 2014
Clinical development of medicinal products intended for the treatment of pain	Draft guideline	EMA/CHMP/970057/2011	Released for consultation May 2013		Deadline for comments 30 November 2013
Development of medicinal products for the treatment of autism-spectrum disorder	Concept paper	EMA/CHMP/40896/2013	Released for consultation April 2013		Deadline for comments 4 July 2013
Clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy	Draft guideline Concept paper	EMA/CHMP/236981/2011	Released for consultation March 2013		Deadline for comments 31 August 2013
Clinical investigation of medicinal products for the treatment of multiple sclerosis	Draft guideline	CHMP/771815/2011 Rev. 2	Released for consultation October 2012		Deadline for comments 9 April 2013
Clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia	Overview of comments Adopted guideline Draft guideline Concept paper	CHMP/40072/2010 Rev. 1	October 2012	1 April 2013	

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History of the Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis

- **1st Guideline** — **1998**
- **2nd Guideline** — **2006**
- **Concept Paper** — **05-2011**
  - Target Population
  - Study design, long-term
  - Biomarkers, endpoints
  - Add-on, combination therapy
- **Draft Guideline** — **10-2012**
- **EMA Workshop** — **10-2013**
- **Final Guideline** — **Q2 of 2015**

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Addressing the regulatory and scientific challenges in multiple sclerosis – a statement from the EU regulators

Balabanov P et al.: Multiple Sclerosis Journal (2014) 20(10) 1282-87

- **First official position from EU regulators, presenting main expected guidance changes**
- **EMA Workshop:**

  „To make sure that in the revision of the MS guideline, the EMA can take the most up-to-date, state-of the-art scientific developments in MS into consideration, as well as the positions of experts in the field on the main topics in the guideline“

- **Identified issues as being of special relevance:**
  - New outcome measures in MS
  - New aspects of disability for the MS patient
  - Patient-reported outcomes (PROs) and their role
  - Use of placebo and biomarkers in MS
  - Recommended approach for investigation of new drugs in MS

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Benefit-Risk Assessment

- **Benefit**
  - Optimized for proof of efficacy
  - Uncertainties/Limits:
    - possible differences between populations and age groups
    - differential individual response
- **Risk**
  - Side effects, interactions, toxicity, potential for misuse
  - Uncertainties/Limits:
    - limited number of study patients
    - possible differences between populations and age groups
    - limited time of active treatment
- **In comparison to identical / similar /comparable medicinal products (supportive)**

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Treatment Goals in Multiple Sclerosis (MS Guidance)

- **Treatment of acute relapse** **(RRMS, SPMS with superimposed relapses, CIS)**
  - Shorten their duration
  - Reduce severity
  - Preventing sequelae
- **Disease Modification**
  - Prevention or delay of accumulation of disability
  - Prevention or modification of relapse
- **Symptomatic improvement of residual disability**

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Multiple Sclerosis – Disease Modification

- **Disability in relation to**
  - Accumulation with relapses
  - Progression in SPMS and PPMS
- **Primary Endpoints**
  - Time to relapse / Annualized relapse rate
  - Progression of disability

⇒ **Relapse-based primary endpoint: no surrogate for disease progression**

⇒ **If primary endpoint is based on relapse assessment: disability progression requested as key secondary endpoint!**

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Multiple Sclerosis – Disease Modification

- **Secondary Endpoints**
  - Progression of disability
  - Relapse rate
  - MRI derived parameters
  - Absence of disease activity
  - Global Measures
  - Outcomes like cognition, fatigue and others
  - Patient reported outcomes (PRO)
  - …

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Multiple Sclerosis – Disease Modification

- **Long-term outcomes (LTOs):**
  - Relevant for chronic disease
  - Most important: development of secondary progression (SP)
  - Do we use the right parameters?

- **Relapse-oriented outcomes**
  - Constructive in MS studies?
  - Relapse prevention still a worthwhile outcome in view of its impact on MS patients

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Methods to Assess Disability in MS: Kurtzke's Expanded Disability Status Scale (EDSS)

- Rating scale
- Non-linear ordinal scale in which the same amount of change (e.g. 1.5 points) signifies a different clinical result in different parts of the scale

  → interpretation of clinical relevance difficult
- Mostly based on standard neurological examination
- Some scores are heavily influenced by motor abilities (with higher scores based predominatly on walking ability)
- Upper limb function and cognitive impairment weakly addressed
- Major issue: Dimensionality of EDSS (clear variability among assessors, lack of responsiveness to chance)

  → appears that patient „remains" on same disability level for long time

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Methods to Assess Disability in MS: EDSS

- MS specialists and regulators are familiar with EDSS
- Historically most frequently used clinician assessment of neurologic impairment in MS clinical trials
- Amount of existing data
- Still important to allow comparison among trials

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Methods to Assess Disability: Scripps Neurological Rating Scale

- Rating scale
- In comparison to EDSS more emphasis on bulbar and upper limb function
- Insensitive to MS-related cognitive change and visual dysfunction
- Clear rationale for the weightings of the various components is lacking
- Less often used in MS trials

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Methods to Assess Disability:

- **Functional walking tests**
  - Timed 25-Foot Walk test (T25-FW)
  - 6-min walking test
  - 12-item multiple sclerosis walking scale (MSWS-12)
- **Ambulation Index**
  - Rating scale based on the T25 FW and patient report
- **Ashworth Scale**
  - Assesses spasticity

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Methods to Assess Disability: Multiple Sclerosis Functional Composite (MSFC)

- Quantitative neurological performance test
- Includes ambulation, upper extremity function and cognition (T25FW+ 9HPT+PASAT combined into a composite z-score)
- Use in clinical trials along with EDSS

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Methods to Assess Disability: new measurement tools

- Alternative tools to EDSS are currently being developed
- Relevant approach: application of functional assessments for measuring disability in MS
- Requirements for new tools:
  - reliable
  - valid
  - sensitive to change over time
  - predictive value for disability progression
  - clinically meaningful
  - acceptable by patient

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Methods to Assess Disability: new endpoints

- New approaches are strongly encouraged!
- EMA intends to apply a flexible approach with regard to the acceptability of positive new endpoints, ready to consider innovative methods
- Prerequisite: scientific justification and adequate validation
- Qualification procedures recommended

⇒ **EDSS will be essential in the following years to allow for direct comparison of future and present/past studies where EDSS has been the key efficacy parameter**

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Patient reported outcome (PRO) measures

- Any outcome evaluated directly by the patient himself and based on the patient`s perception of a disease and its treatment
- To evaluate: e.g. quality of life (MSQL), fatigue (MFIS), walking (MSWS-12), pain (MOS-PES), depression (HDRS)
- Importance of its use in clinical development adressed by patient representatives

⇒ **Collaborative work necessary by academia, industry and regulators to develop criteria for appropriate use of PROs in studies, for instance to help assessing clinical relevance**

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Pre-authorisation
Post-opinion
Post-authorisation
Product information
Scientific advice and protocol assistance
How to submit a request
Fees and fee reductions
Novel methodologies / biomarkers
Guidance
Scientific guidelines
Innovation Task Force
SME office
Paediatric medicine
Geriatric medicine

Home ▸ Human regulatory ▸ Scientific advice and protocol assistance ▸ Novel methodologies / biomarkers

Qualification of novel methodologies for medicine development

Email Print Help Share

The European Medicines Agency offers scientific advice to support the qualification of innovative development methods for a specific intended use in the context of research and development into pharmaceuticals.

The advice is given by the Committee for Medicinal Products for Human Use (CHMP) on the basis of recommendations by the Scientific Advice Working Party (SAWP). This qualification process leads to a CHMP **qualification opinion** or CHMP **qualification advice**.

CHMP qualification opinions

The CHMP can issue an opinion on the **acceptability of a specific use of a method**, such as the use of a novel methodology or an imaging method in the context of research and development. The method can apply to non-clinical or to clinical studies, such as the use of a novel biomarker.

The opinion is based on the assessment of data submitted to the Agency.

Before final adoption of qualification opinion, the CHMP makes its evaluation open for **public consultation** by the scientific community. This ensures that the CHMP shares information, as agreed with the applicant, and is open to scientific scrutiny and discussion.

CHMP qualification advice

The CHMP can issue **advice on protocols and methods** that are intended to develop a novel method with the aim of moving towards qualification.

The advice is based on the evaluation of the **scientific rationale** and on the **preliminary data** submitted to the Agency.

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Fampridine

- Indicated for the improvement of walking in adult patients with MS with walking disability (EDSS 4-7)
- Primary objective: to assess the efficacy (assessment by walking speed improvement) in patient with MS
- Walking speed based on the T25FW Test
- Secondary endpoints: 12-Item MS Walking Scale, Lower Extremity Manual Muscle Testing score, Ashworth Spasticity Examination score
- Observed benefit: ability to improve walking speed, as measured by T25FW Test

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Fampridine

- To which extent represents walking speed walking ability, walking quality, endurance and range of action?
- Re-examination
- Conditional marketing authorisation
  - more evidence needed on long-term effects on other aspects of walking ability beyond the effect on walking speed (e.g. balance, endurance, walking distance)

⇒ **Condition: Long-term study to investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment**

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Ataluren

- Indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older
- Primary objective: to determine the effect of ataluren on ambulation
- Secondary objectives: to evaluate the effects of ataluren on physical function, patient-reported outcomes, cognitive function, cardiac function….
- Primary endpoint: change in 6MWD from baseline to Week 48
- Results on secondary endpoints did not support primary endpoint: clinical relevance? clinical efficacy not sufficient

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Ataluren

- Re-examination:
  - Based on arguments of applicant and all supporting data CHMP re-examined its initial opinion: risk-benefit balance is favourable

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Summary

- **MS Guideline is under revision, final guideline update probably by the middle of the year**
  - Results from workshop are considered
- **Open to new endpoints**
- **EDSS also needed in next future**
- **PROs: Collaboration needed to develop criteria for appropriate use in studies**
- **Use of scientific advice/ qualification procedures!**

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