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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## Concept paper on no need for revision of the guideline on medicinal products for the treatment of Alzheimer's disease and other dementias

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End of consultation (deadline for comments)	n/a

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## 1. Introduction

Despite the rapid progress in understanding of the neurobiology and pathophysiology of Alzheimer's disease (AD) only cholinesterase-inhibitors and memantine have been approved for the symptomatic treatment with overall limited clinical improvement. Whereas in other diseases (Parkinson's disease) longer lasting symptomatic improvement effects are much more impressive compared to AD, yet no product has been approved for disease modification in any neurodegenerative disorder by regulatory bodies. Unfortunately, many clinical trials recently failed to show symptomatic improvement or promising hints for disease modification in AD, e.g. medicinal products with an A $\beta$ -targeted mode of action.

There are now many activities leaving the concept of the full picture of dementia as a first step of diagnosis for AD. This will require new standardisation of diagnostic criteria particularly for earlier disease stages. In consequence new validated assessment tools sensitive to change in the different dimensions of AD are necessary in earlier stages of the disease. If a treatment claim for disease modification is strived for, it has to be shown that the treatment has an impact on the underlying pathophysiology of AD in addition to clinical improvement. This will lead to more complex study designs (adaptive designs, staggered start and withdrawal designs, combination of symptomatic and potential disease modifying compounds, etc.). In addition the progress in qualification and validation of biomarkers might play an important role in future drug development for AD, and regulatory requirements in this process should be specified based on recent scientific advice procedures.

## 2. Problem statement

Two major issues are important for assessment of future clinical trials in AD and other dementias:

1. the change of diagnostic criteria and their validation;
2. the potential use of biomarkers in the different stages of drug development.

Recently several papers on new diagnostic criteria for AD have been published. Although full validation of these research criteria has not been finalised they are already being used in ongoing clinical trials.

Moreover, several biomarkers including genetic markers, cerebrospinal fluid markers and brain imaging markers (MRI, PET, SPECT) have been studied extensively and are under evaluation. Shortly new evidence from finalised clinical trials and large research consortia like ADNI will be published on the potential use of biomarkers. Consequently, numerous scientific advices have been given for development programs on medicinal products for treatment of AD and recently SAWP published qualification opinions on the use of cerebrospinal fluid markers and hippocampal MRI for enrichment of study populations with patients at risk for or with AD.

## 3. Discussion (on the problem statement)

The following critical aspects should be discussed in a future update of the guideline:

- The impact of new diagnostic criteria for Alzheimer's disease and other dementias on clinical trial design.
- The choice of outcome parameters and need for distinct assessment tools with regard to the different disease stages in AD and other dementias (different signs and symptoms, differences in change over time, severity).

- Assessment of efficacy and safety in different age groups (e.g. old versus very old).
- Potential use of biomarkers and their temporal relationship with the phases of AD in different stages of drug development (mechanism of action, use as diagnostic test, enrichment of study populations, stratification for subgroups, safety and efficacy markers, etc.).
- Design of long-term efficacy and safety studies.
- Usefulness of combination therapy and corresponding study designs.

All pertinent elements outlined in current and future EU and ICH guidelines and regulations should also be taken into account.

## **4. Recommendation**

CHMP is well aware of the ongoing clinical trials and validation studies of new diagnostic criteria and potential biomarkers. However, it seems premature to update now the current "Guideline on Medicinal Products for the Treatment of Alzheimer's Disease and Other Dementias". As soon as new validated data on diagnostic criteria and potential biomarkers will be available these scientific developments and current experience in SAWP procedures will be taken into consideration for an update of the Guideline on Medicinal Products for the Treatment of Alzheimer's Disease and Other Dementias. Therefore postponement of the update is recommended by CNSWP.

## **5. Proposed timetable**

Reconsideration of an update of the CHMP guideline might take place in 2013.

## **6. Resource requirements for preparation**

Currently expert consultation is not required. In case of updating the guideline this will be reconsidered depending on the new data and evidence available. The preparation of a future update will involve the CNSWP. Two rapporteurs from the CNSWP will be involved; drafts of the document will be discussed with BSWP, SAWP and other WPs as appropriate.

## **7. Impact assessment (anticipated)**

As outlined currently an update of the guideline document is considered premature due to the ongoing basic and clinical research. If these newer data will be available an updated "Guideline on Medicinal Products for the Treatment of Alzheimer's Disease and Other Dementias" will be helpful to achieve consensus in the evaluation of such products by regulatory authorities in the European Community. Furthermore, it is expected, that such guideline would improve quality and comparability of development programs for this specific indication by pharmaceutical companies.

## **8. Interested parties**

The interested parties in the guidance document include learned societies and academia (e.g. European College of Neuropsychopharmacology (ECNP); Alzheimer's Association; European Alzheimer's Disease Consortium (EADC) and others), pharmaceutical industry (e.g. EFPIA and others) and other regulatory agencies.

## 9. References to literature, guidelines, etc.

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