EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Scientific Advice throughout the life-cycle of the product

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Scientific Advice

Advising Applicants on the scientific requirements for marketing authorisation :

- Before the first marketing authorisation (MA): companies ask questions on manufacturing, non-clinical and clinical trials, risk-management plans, ways to develop generics and biosimilars; significant benefit for orphan medicines; development in children.
- Post-MA: extension of indication to different age groups and stages of the disease; different conditions; & safety aspects.

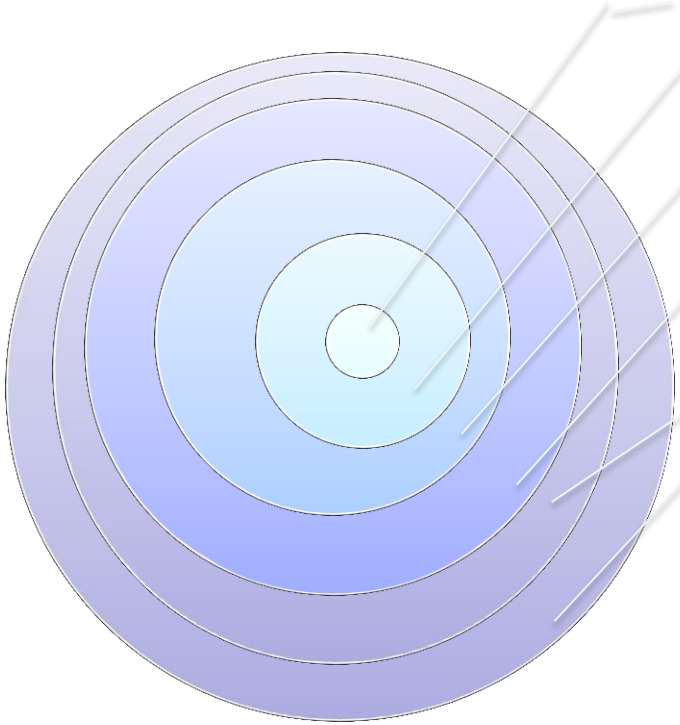
Scientific Advice Working Party of the Committee for Human Medicinal Products (CHMP)

- 30 experts from national authorities, universities and hospitals selected for expertise: e.g. oncology, cardiology, psychiatry, neurology, immunotherapy, gene and cell therapy, pediatrics, geriatrics; quality, non—clinical and statistical methodologies.
- Joint members across Committees not only CHMP, but also Paediatrics, Orphan, Advanced Medicinal Products
- Scientific and logistic support from EMA secretariat: 10 medical doctors /pharmacists and 7 assistants

Scientific Advice Working Party of the Committee for Human Medicinal Products (CHMP)

- 3-4 day meetings per month (except August)
- Networking many thousands of EU experts

Scientific Advice Network



SAWP - Multidisciplinary expert group

Scientific secretariat

External experts /Clinicians

CHMP, WPs and other Committees

Patient organisations

Health Technology Assessment Bodies

Scientific advice: Procedure

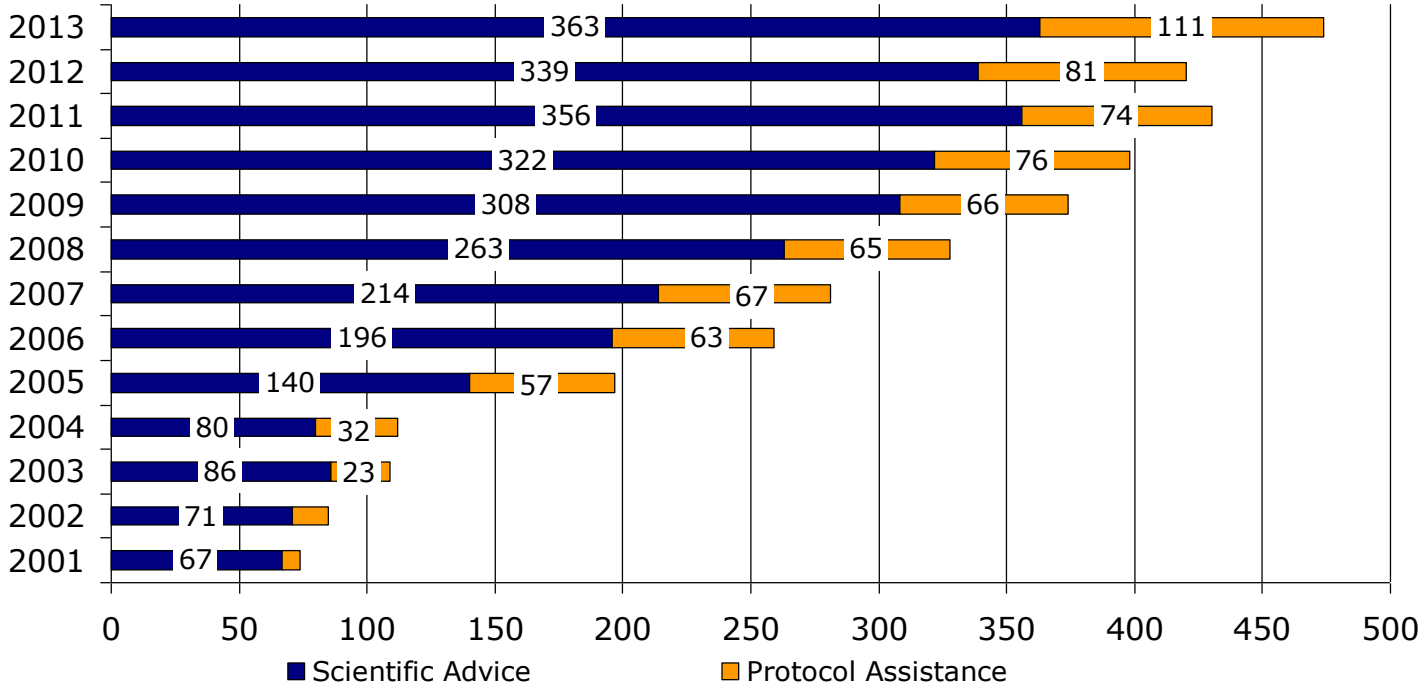
Voluntary, not mandatory procedure:

- **Pre-submission meetings**: guidance to companies on how to formulate questions and company's position and l scientific steer on what can be expected.
- In meeting possibility to discuss also regulatory questions with follow up in writing from the regulatory affairs team
- ~ 200 meetings per year

Scientific advice: Procedure

- Responses to the scientific questions are prepared and discussed;
- In 50% of the cases, in particular when the experts do not agree with the company's proposal, a face-to-face meeting with the company is organised.
- Final written responses are discussed and adopted by the CHMP and sent to the company: **scientific advice letter**
- **short procedure: 40 days or 70 days** when a face-to-face meeting takes place.

Scientific Advice main activity so far: scientific advice and protocol assistance for orphan drugs



Qualification of Novel Methodologies

- **Vision**: Speed up/optimise drug development and utilisation, improve public health
- Procedure to guide the development of new more efficient ways to develop drugs, e.g. development of new endpoints for clinical trials:

  E.g. Can changes in chemicals (biochemistry) or structures (imaging/MRI) in the brain predict the development of Alzheimer's disease before the patients lose their memory and cannot function so that a medicine can intervene early on and be more effective?

- Started 2008: 60 procedures so far

Qualification of Novel Methodologies for drug development

CHMP Qualification Advice on future protocols and methods for further method development towards qualification.

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.

Who can apply? Consortia, Networks, Public / Private partnerships, Learned societies, Pharmaceutical industry.

Qualification of Novel Methodologies

Methods to predict toxicity

Inclusion criteria to enrich a patient population for a clinical trial: Volume of certain brain structures and level of certain biochemicals in the cerebrospinal fluid for trials in Alzheimer's disease

Surrogate clinical endpoints: new sensitive scales to measure efficacy of a new drug instead of hard clinical endpoints

Patient and caregiver reported outcomes

Qualification of Novel Methodologies

Preclinical development

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

Clinical development

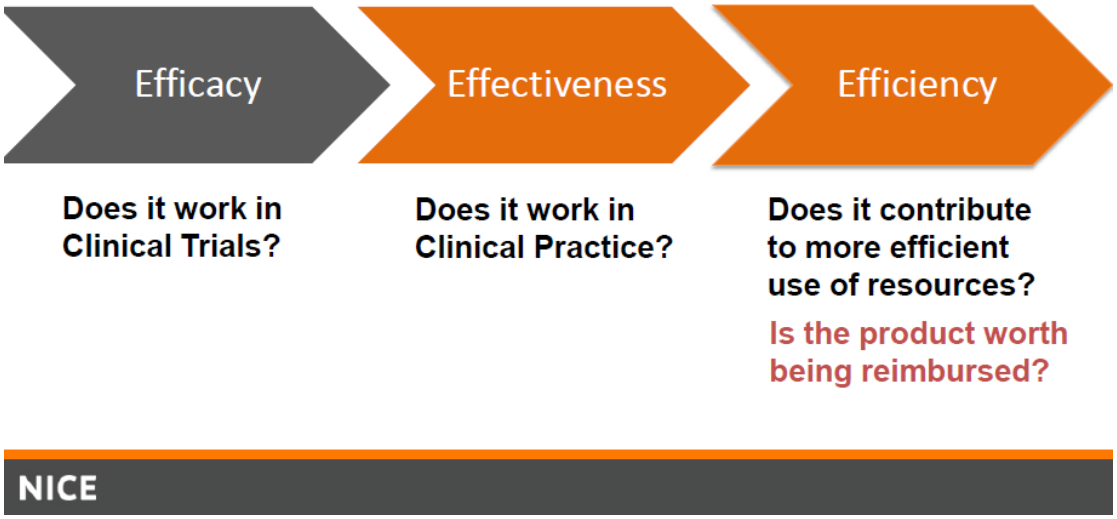
- verify mechanism
- dose-response
- proof of concept
- **enrich population**
- **surrogate endpoint**
- Early detection of safety signals

Drug utilisation

- optimise target population
- guide treatment regimen

Role of Health Technology Assessment Bodies

Triple E of Health Technologies



Acknowledgment:
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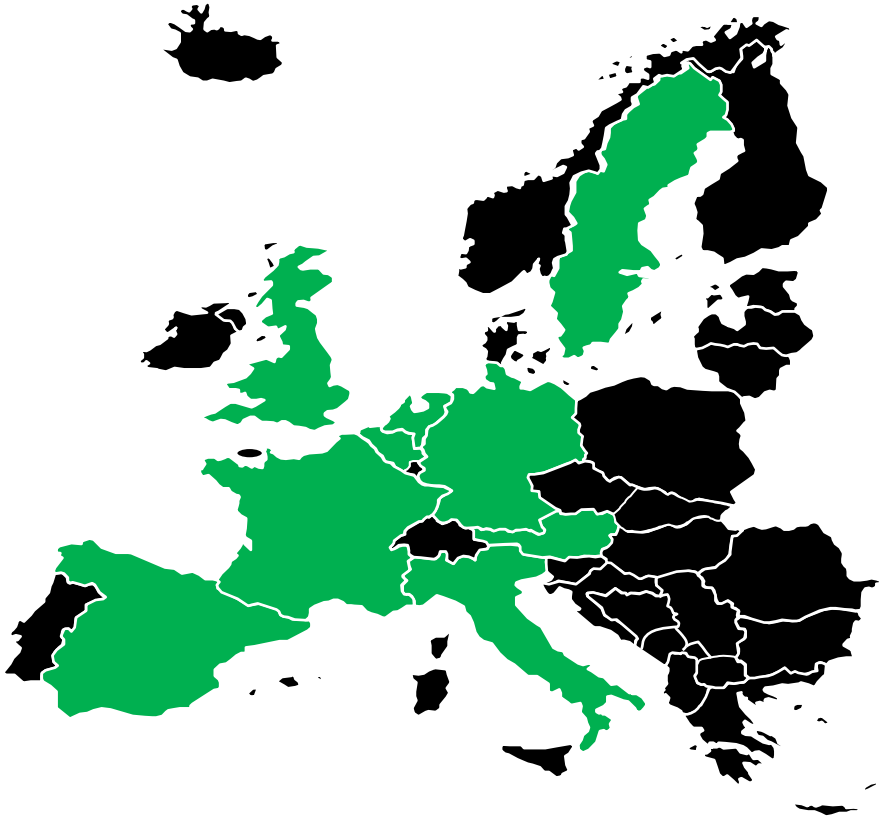
Scientific advice together with health technology assessment bodies

- Possibility for Applicants to discuss together with Regulators and Health Technology Assement bodies (HTAs) early in development what is needed to not only for the benefit/risk asessment (Regulators) but also decide on the added value (HTAs) so that HTAs recommend reimbursement and the product gets to the patients.
- Started 2010: 34 procedures so far, HTAs from UK, Italy, France, Sweden, Germany, Spain, Netherlands, Belgium
- Workshop on the 26th of November 2013 attracted more than 300 participants: regulators, HTAs, Industry, SMEs, Academia, Health Care Professionals, Patient representatives, European Commission.

EMA HTA Parallel SA: Experience to date

- **34 parallel EMA – SA procedures** with EU HTA bodies from UK, Italy, Germany, Sweden, France, Netherlands, Spain, Belgium

- **Broad range of indications**: Lung cancer, Breast cancer, Pancreas cancer, Melanoma, Asthma, COPD, Diabetes, Heart Failure, Depression, Alzheimer's, Infections, Rare diseases



Parallel HTA/EMA SA - Experience so far

- Diabetes, Heart Failure
- Alzheimer's, Depression
- Lung Cancer, Breast Cancer, Melanoma, Pancreas-Ca, Mesothelioma, Leukaemia, Cachexia in cancer
- Asthma, COPD, Rheumatoid Arthritis, Osteoporosis
- Multi-resistant Infections,
- Food Allergies, 2 Gastroenterology conditions
- Orphan conditions; Cell therapy; Ophthalmology

The majority are new mechanisms of action in the respective area, new monoclonal antibodies, new chemicals, tumour vaccines.

Parallel HTA/EMA SA - Experience so far

Common discussions: Elements which are necessary for the benefit/risk assessment (Regulators) and added value (HTAs)

- Comparator: placebo, active comparator
- Clinical endpoints: Survival, quality of life
- Duration of the trial
- Patient population to be included premarketing / post marketing

EMA/HTA: Novel Therapy for COPD

- Company proposed a licensed comparator
- EMA agreed with licensed comparator
- HTA want to be able to compare value of new therapy compared to what it will replace, even if comparator is not licensed for use

Solution: Introduction of new arm to pivotal study to include both options

EMA/HTA: 2nd line treatment for a rare cancer

- No product authorised
- Company proposes placebo as control
- EMA agrees
- One HTA body requests a particular active comparator used in their country albeit not authorised
- 2nd HTA body requests placebo, they cannot accept by law a non authorised comparator

Solution: Comparator Investigator's best choice

Parallel EMA/HTA SA

Questions for the HTAs only: Impact on the caregiver

- Do the Stakeholders consider the impact to the caregiver (e.g. time assisting or supervising patient) an important piece of the value proposition when evaluating a treatment for prodromal Alzheimer's disease?

- Do the Stakeholders agree with the selection of instruments in the clinical trial to capture the burden to the caregiver (Dependence Scale)? Are there any other data that should be collected?

- Overall cost-effectiveness of the product:

  - delaying progression may also extend life expectancy
  - Modelling is necessary to project out the implications of potential post-trial scenarios

Parallel EMA/HTA SA

Questions for the HTAs only: Modelling of disease

- The economic evaluation for a drug that slows or delays the progression of Alzheimer disease (AD) relies on the evaluation of the costs attributable to AD had it progressed to more severe stages. As the Phase 3 clinical program may not be long enough to capture the course of the disease, do the HTAs agree that other clinical trial data may be used to model the natural course of AD across time?

Parallel EMA/HTA SA

Questions for the HTAs only: Early use of new antibiotics

- Company argues that appropriate use of new, higher cost antibiotics as initial empiric therapy delivers greater overall benefits to health systems than holding them in reserve. Whilst doing so may result in short term increases of drug acquisition costs, this approach will minimise longer-term societal costs due to a reduction in the emergence of resistance, and the potential to prolong the utility of all antibiotics. What is the view of the participant HTAs?

EMA/HTA: Ongoing activities

- 5 Parallel EMA-HTA procedures ongoing
- EMA-HTA group works on procedure to be published for consultation
- EMA participates also in the SEED Consortium (Shaping European Early Dialogues), led by the French Haute Autorité de Santé (HAS), who won the EC Call for Tender: 14 HTA bodies, 7 procedures on Medicinal products planned for 2014.
- EMA is associated with the newly convened HTA Network (HTAN) of the EC

EMA HTA Parallel SA: Experience to date

- Workshop on the 26th of November 2013 attracted more than 300 participants: regulators, HTAs, Industry, SMEs, Academia, Health Care Professionals, Patient representatives, European Commission
- May 2014: Procedure in the EMA web-site

Parallel scientific advice with health-technology-assessment bodies

The Agency also offers parallel scientific advice with health-technology-assessment (HTA) bodies. The aim of this is to allow medicine developers to gain feedback from from regulators and HTA bodies at the same time, early in the development of a medicine. This helps them to establish the evidence that both parties will need to determine a medicine's benefit-risk balance and value.

A pilot for parallel scientific advice was launched in July 2010. Around 25 procedures had been finalised or were ongoing as of November 2013, covering indications such as diabetes, heart failure, lung cancer, breast cancer, pancreatic cancer, melanoma, mesothelioma, asthma, rheumatoid arthritis, multiresistant infections, food allergies, diabetic gastroparesis, Alzheimer's disease, depression, osteoporosis and three rare conditions.

EMA/HTA: EMA-EunetHTA 3 year program

- Scientific advice/early dialogue involving regulators and HTAs.
- Scientific and methodological guideline development.
- Post-licensing (post-authorisation) data generation.
- Availability of clinical study data.
- Orphan medicinal products.
- Cooperation in specific pilot projects of EUnetHTA JA2.
- Conferences, workshops and seminars/meetings
- EMA-HTA group works on procedure to be published for consultation

Scientific Advice – Challenges

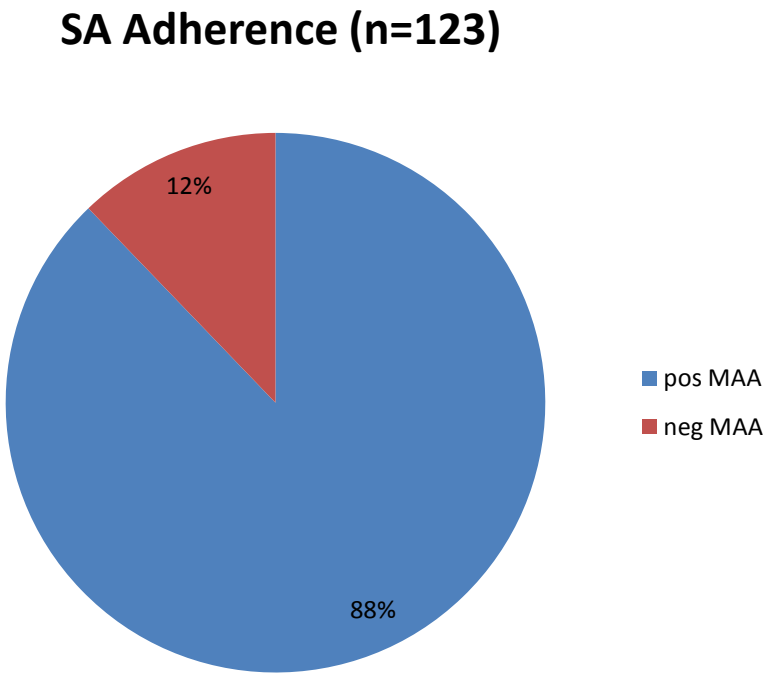
- Reinforce SA throughout the life-cycle of the product: currently (only) 25% of the SA procedures are for products which have an initial MA.
- Integrate better Health Technology Assessment Bodies including parallel SA with HTAs peri and post licencing.
- Integrate better also other Stakeholders like Patient Representatives, Health Care Professionals, Academics , Learned Societies.
- Integrate better Modelling & Simulation (through the newly formed M&S Working Group) throughout the life-cycle of the product

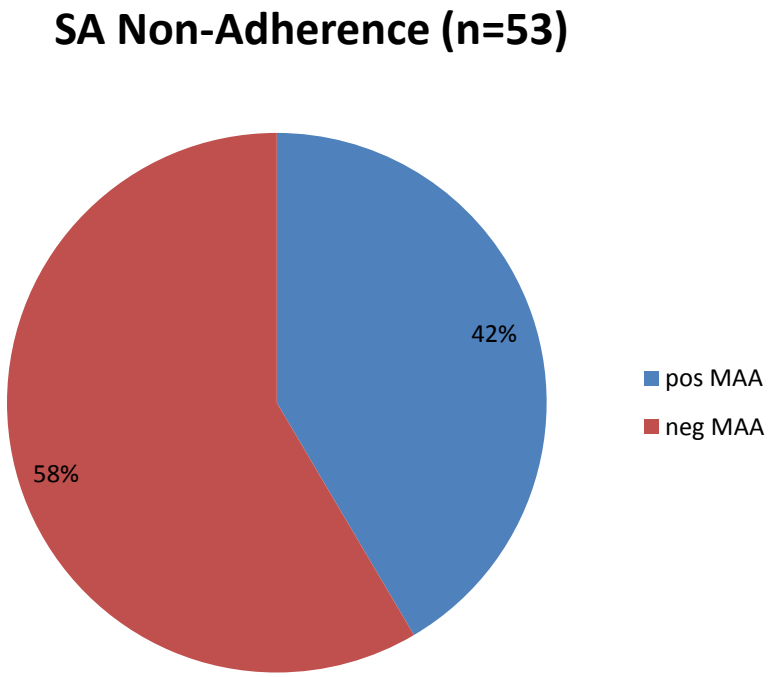
Scientific Advice - Impact

More than 70% of the Marketing Authorisation Applications coming to the Agency have received SA during the development.

Obtaining and complying with Scientific Advice is strongly associated with a positive outcome of a Marketing Authorisation application: almost 90% of those who obtain and follow SA receive a positive opinion compared to 40% for those who do not follow SA.

Positive impact of SA adherence on MAA outcome





Thank you

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