EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Scientific advice and its impact on marketing authorisation application reviews

SME info day: Tools to support innovative medicines' development and early access

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Scientific Advice Office

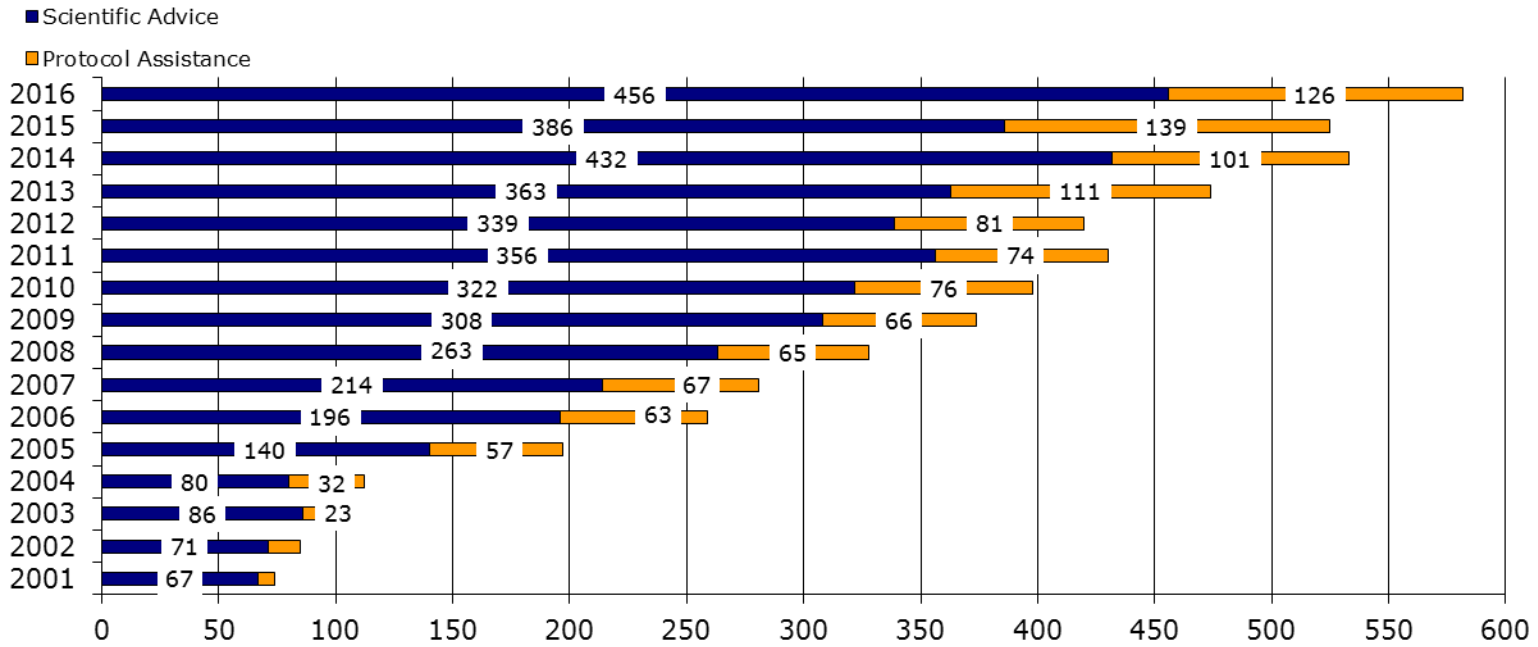
Objective of Scientific Advice (SA)

- The overall attrition rate for developing a drug is currently calculated to be 10,000:1.
- The average cost of bringing a drug to the market is approaching 1 billion dollars.
- Increased regulatory requirements/scrutiny

Support sponsors to generate adequate data for the benefit–risk assessment at the time of MAA, and thereby facilitate the introduction of new, safe and effective medicines.

…but does it work?

Requests for Scientific Advice over time



Scientific Advice – General principles (1/2)

- Legal basis: According to Article 57-1 (n) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004
- One of the tasks of the Agency is "advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products".
- Advising Applicants on the scientific requirements for marketing authorisation (MA):
  - Before the first MA: companies ask questions on manufacturing, non-clinical and clinical trials, risk-management plans, ways to develop generics, hybrids and biosimilars; significant benefit for orphan medicines; development in children etc.
  - Post-MA: extension of indication to different age groups and stages of the disease; different conditions; & safety aspects. Line extensions etc.

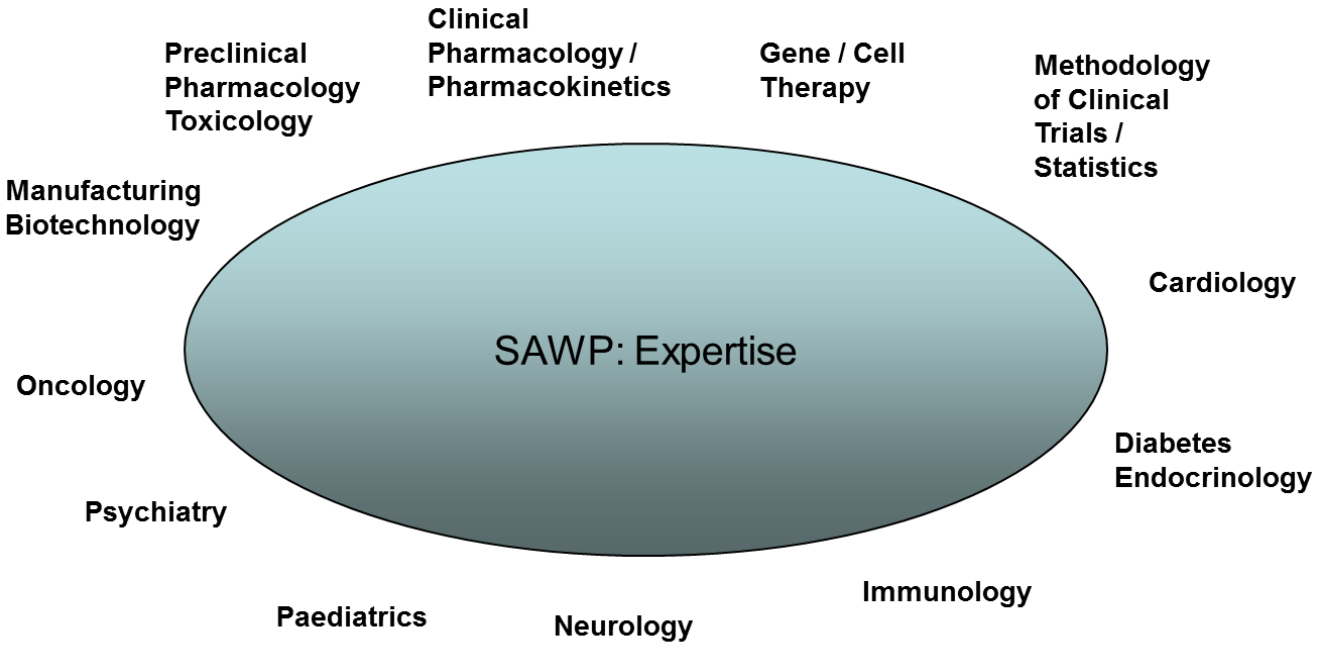
Scientific Advice – General principles (2/2)

- For human medicines, SA and protocol assistance are given by the Committee for Medicinal Products for Human Use (CHMP) on the recommendation of the Scientific Advice Working Party (SAWP).
- Prospective in nature- focusing on development strategies rather than pre-evaluation of data to support a MAA.

Scientific Advice Working Party (SAWP)

- A WP of the CHMP that meets 11 times a year for a 3-4 day meeting.
- A Multidisciplinary Expert Group and includes the Chairperson and up to 36 members. Membership is based on complimentary scientific expertise - not on nationality.
- Some SAWP members are also members of the CHMP, COMP, PDCO, CAT, PRAC, SWP, BWP etc.
- Access to a network of European experts. Interactions with the FDA, HTAs, WHO and patient organisations.
- All advice given is extensively peer reviewed and approved by the CHMP. The SA given reflects evidentiary standards that the CHMP will apply by the time of MAA to establish whether there is a positive benefit/risk or not.

Scientific Advice Working Party (SAWP)



The Scientific Advice procedure

A streamlined 70-day procedure (maximum) with possibility of finalisation in 40 days. Several opportunities for interactions.

SA can be given on any scientific question

- Quality, non-clinical and clinical or Broad advice
- In parallel with the FDA (WHO)
- In parallel with HTAs/payers/patient organisations/academics
- Advice and Opinion on Qualification of novel methodologies/biomarkers
- Regulatory issues can be addressed a Pre-submission meetings

SA can be requested at any time point of development

- Post-marketing advice is also available
- Paediatric SA during PIP procedure (with PDCO agreement)
- Allow sufficient time to address modifications

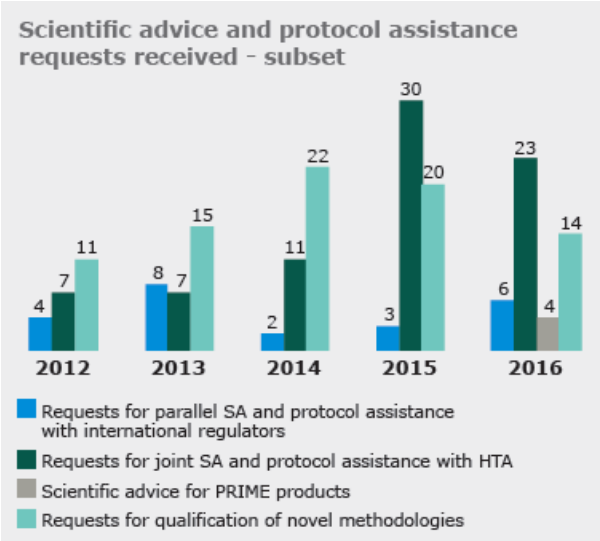
Not legally binding but scientifically applicable throughout the EU

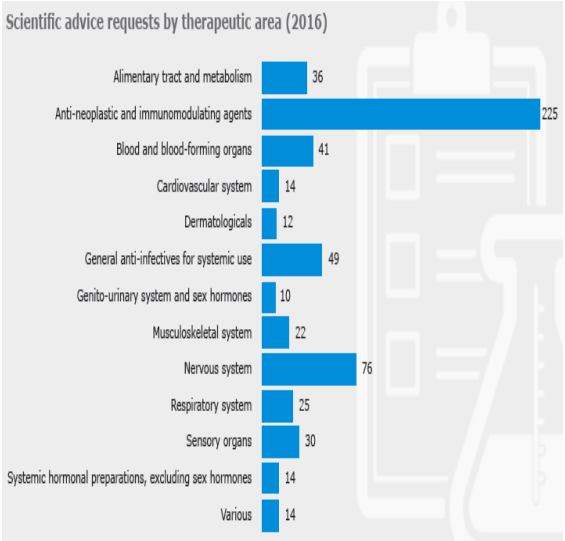
Guidance for „Scientific Advice“ on the EMA website

Available on the website:

- European Medicines Agency guidance for applicants seeking scientific advice and protocol assistance, EMA/4260/2001 Rev 9
- Briefing document template
- Template letter of intent

Most common Scientific advice requests





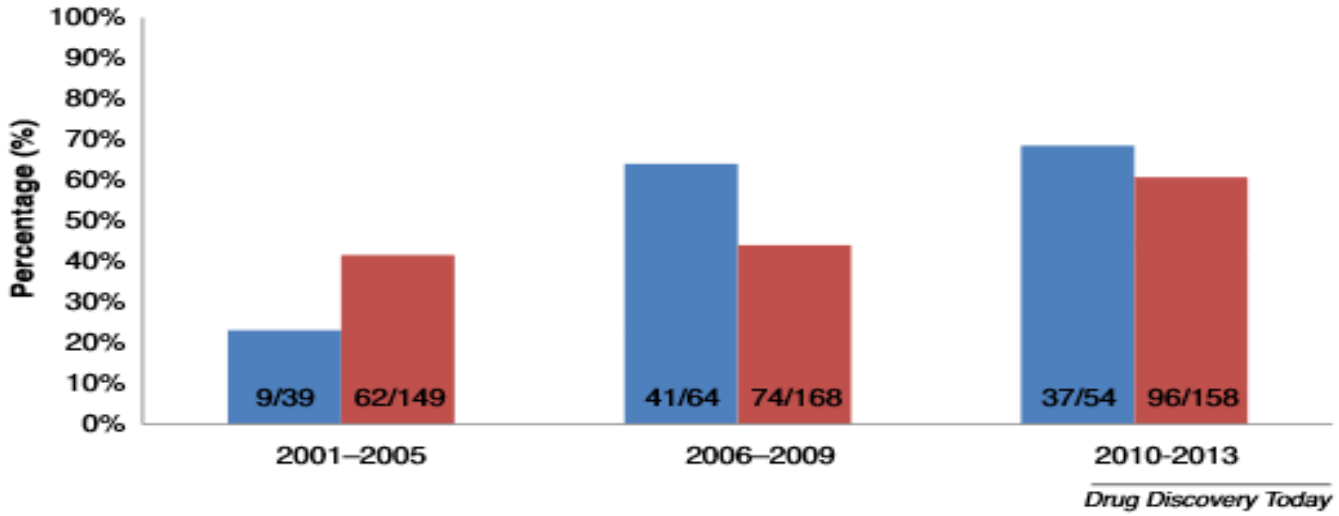
Source: EMA Annual Report 2016

- More than half of requests for scientific advice relate to clinical issues, over one in four to preclinical issues, and the rest to quality issues
- In 2016, 56% of requests related to medicines in phase III and 27% to medicines in phase II of their clinical development

Publications addressing factors associated with MAA outcome (2004 – 2013)

1. Factors associated with success of marketing authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Regnstrom et al. Eur J Clin Pharmacol (2010) 66: 39-48.
2. Regulatory watch: Impact of scientific advice from the European Medicines Agency. Hofer et al. Nature reviews Drug Discovery (2015) 14(5).
3. Marketing authorisation of orphan medicines in Europe from 2000 to 2013. Hofer et al. Drug Discovery Today. October 2017.

Analysis of MAAs with an outcome between 2000 -2013: Proportion of MAAs that have received SA



Analysis of MAAs with an outcome between 2004 - 2007: Factors associated with outcome

Significantly associated in simple logistic regression analysis:

Company size* OR (95% CI)=2.96 (1.93, 4.56)

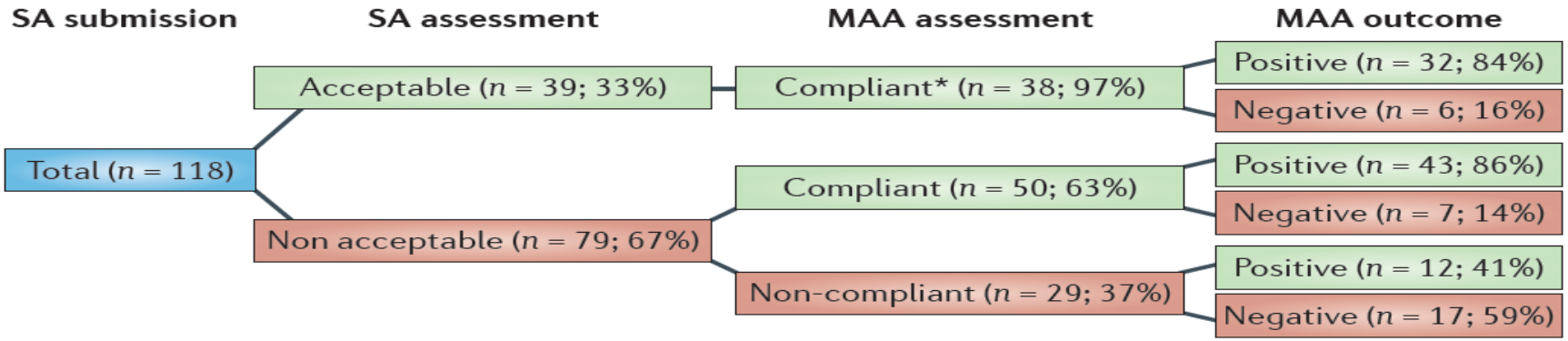
Orphan status, OR (95% CI)=0.38 (0.19, 0.77)

Compliance with SA* - concerning 3 critical clinical issues in pivotal phase 3 studies; primary endpoint, comparator, statistical analysis, OR (95% CI)= 14.71 (1.95, 111.16)

Year of MAA, product type, or therapeutic area not associated with outcome.

*significant association in multiple regression analysis

SA can help to guide changes in the pivotal clinical development towards improved regulatory acceptability



- Obtaining and complying SA is strongly associated with a positive outcome of a MAA: almost 90% of those who obtain and follow SA receive a positive opinion compared to 40% for those who do not follow SA; *Hofer et al. 2015*

Qualification of novel methodologies and biomarkers

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

Examples:

- Methods to predict toxicity; IC 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 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.

117 procedures since start in 2008

Conclusions and recommendations (1/2)

- Company size is an important predictor of outcome
  - Resources, experience etc.
- Compliance with SA associated with outcome
  - SA reflects standards CHMP will apply by the time of MAA to assess benefit/risk
  - Larger pharmaceutical companies more frequently ask for SA and are more compliant with SA
  - Small companies predominantly developing orphan drugs are less compliant

Action taken by the EMA:

SMEs - Financial & administrative assistance
  - SME office
  - Fee reductions

The COMP and OD secretariat at EMEA
  - Fee reduction for PA

Conclusions and recommendations (2/2)

►Encourage SA/ FU SA

- Early in development and at major transition points (critical steps)
- When not complying with previous SA or changing the plan
- When there are no GLs or "state-of-the-art" or when deviating from them
- When there are uncertainties or critical findings
- SMEs and Orphans (Pre-submission meeting)
- Advanced therapies
- Establish a relationship/familiarise regulators
- Enhance probability of successful MAA – if you adhere

►Ask specific questions – avoid open questions. Provide a clear company position. Be open.

►Consider SA from national EU agencies, and EMA/FDA parallel advice, Multi-stakeholder parallel Scientific Advice (HTAs/payers etc)

Any questions?

Further information

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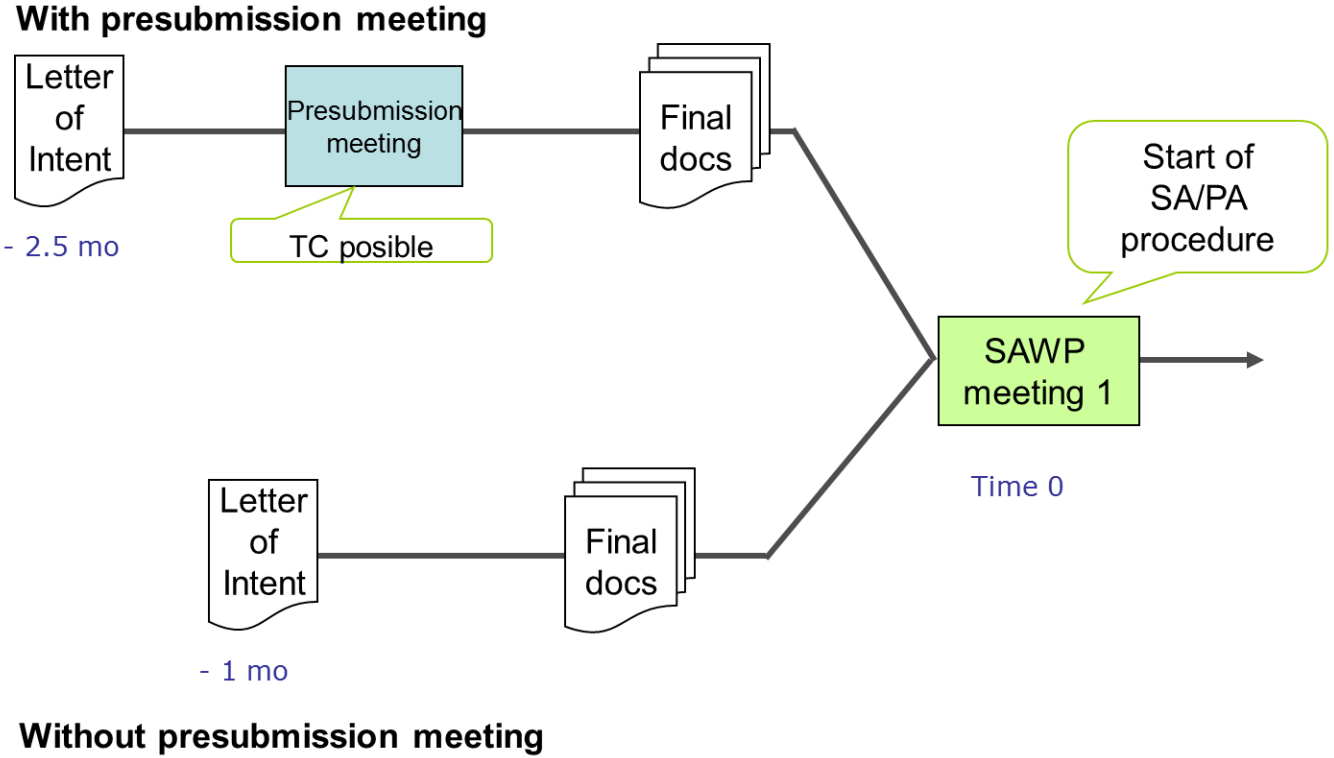
Procedural workflow (1/2)



Procedural workflow (2/2)