EMA Scientific Advice

EIC – EMA Info Day

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Outline

- What is scientific advice
- How EMA scientific advice works
- Variations of the advice process

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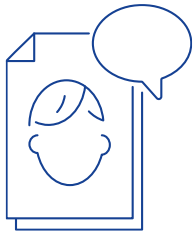
What is scientific advice?



Regulators' advice on the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products

Clarification of scientific requirements for marketing authorisation (MA):

- Manufacture and testing, non-clinical (in vitro and animal) and clinical testing, risk management plans and post-authorisation follow-up (efficacy or safety), methodological aspects (statistics, data analysis, modelling and simulation) etc.
- Type of marketing authorisation, post-authorisation extension of indication, ways to develop generics, hybrids and biosimilars, development in children etc.

Prospective in nature - focusing on development strategies rather than pre-evaluation of data to support a MAA

In the form of specific questions to be answered

Types of questions to ask

- Are the patients to be included in a study sufficiently representative of the population for whom the medicine is intended?
- Are the planned measures to assess the benefits of a medicine valid and relevant?
- Is the proposed plan to analyse results appropriate?
- Does the study last long enough and include enough patients to provide the necessary data for the benefit-risk assessment?
- Is the medicine being compared with an appropriate control?
- Are the plans to follow the long-term safety of the product appropriately designed?

Acceptable and non-acceptable questions

- Perhaps the single most common question being asked is:

  Is a study/set of studies/overall development **plan** adequate to support a marketing authorisation?
  (acceptable as focusing on prospective planning aspect; specific elements should still be detailed)

- On the other hand, the following question is not acceptable:

  Are the phase 3 study **results** adequate to support marketing authorisation?
  (this is pre-assessment of existing data)

- Specifically for paediatric developments, there is a legal requirement for the overall development plan to be agreed with the paediatric committee (PDCO)

  Can the proposed studies support an indication in children above 2 years of age?
  (question for the PDCO, but scientific advice can be sought on the design of individual studies)

What is protocol assistance?

Scientific advice given on the development of orphan designated medicinal products is called protocol assistance

It benefits from fee incentives of the orphan legislation

It can include questions on the plan to demonstrate ‘significant benefit’ of the orphan designated product vs established therapies (pharmaceutical or not) in the target condition which is a requirement for the maintenance of the orphan designation at the time of marketing authorisation (MA)

What is broad scientific advice?

- Scientific advice is product- and indication-specific
- Specific issues affecting multiple products or indications could be treated as single broad advice requests (e.g., quality changes, platform clinical trials)
- No product- or indication-specific questions are accepted in a broad advice

Why ask for scientific advice

- Compliance with scientific advice was repeatedly shown to be a predictor for marketing authorisation success (Regnstrom et al, 2010 – 2004-07 data; Hofer et al, 2015 – 2008-12 data; unpublished 2013-19 data)
- This has also been shown for orphan designated products (Hofer et al, 2018 – 2001-13 data)
- Orphan products and SME applicants are less likely to succeed in their marketing authorisation applications; nevertheless, receiving and complying with scientific advice increases chances of success similarly to non-orphan products and big pharma applicant (Regnstrom et al, 2010, Hofer et al, 2015, Hofer et al, 2018)

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How EMA scientific advice works

Variations of the advice process

The Scientific Advice Working Party (SAWP)

- Standing working party of the Committee for Medicinal Products for Human Use (CHMP) with the sole remit of providing scientific advice
- Meets on a monthly basis 11 times per year (no meeting in early August)
- Consists of 72 members and alternates nominated based on expertise needs including representatives from EMA committees
- For each scientific advice or protocol assistance request, two members are appointed as co-ordinators and at least one member is appointed as peer reviewer
- Requests are additionally referred to other committees, working parties, operational expert groups and working groups for peer review input

How to submit a scientific advice request

Submission occurs using the online platform IRIS

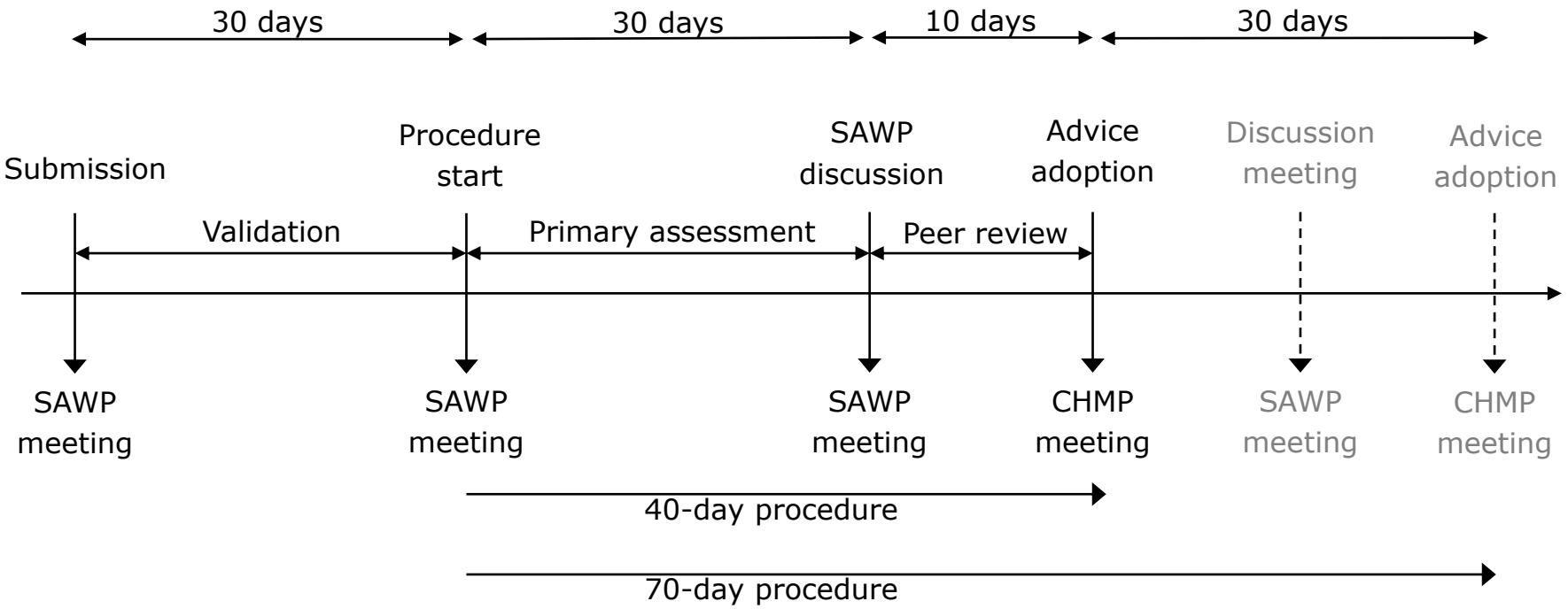
The applicant organisation, contact point, active substance and medicinal product need to be registered with the EMA (refer to the Quick interactive guide to IRIS registration process). In addition, a Research Product Identifier (RPI) needs to be requested, if not available already from prior regulatory interactions

For further information and training:

Online training: how to register for access to IRIS; what research product identifiers (RPI) are and how we use them | European Medicines Agency (europa.eu)

Online training: How to submit initial and follow-up scientific advice applications (human) using IRIS | European Medicines Agency (europa.eu)

The scientific advice procedure



Scientific advice fees

- Dependent on the type and number of areas of advice (quality, non-clinical, clinical)
- Dependent on the initial or follow-up nature of the request
  - Initial request: first request in an indication or subsequent request with additional areas of advice
  - Follow-up request: prior request in the same indication and the same (or less) areas of advice
- Fee incentives for paediatric(-only) developments, protocol assistance, SMEs, ATMPs and PRIME products
- Fee waivers for orphan products from academic applicants and on the clinical development of products addressing public health emergencies

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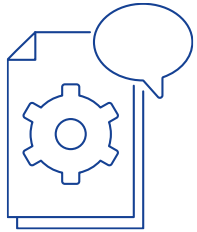
Qualification of novel methodologies and biomarkers

Framework to guide the development of new more efficient ways to develop drugs, e.g. development of new endpoints for clinical trials



Aim: Speed up/optimise drug development and utilisation

Examples:

- Biomarkers to predict toxicity or enrich a patient population
- Surrogate clinical endpoints
- Patient and caregiver reported outcomes
- Patient/disease registries

Relies on meta-analysis of multiple data sources and qualifies the method for use in a specific Context-of-Use

Parallel scientific advice (PSA) with the FDA

- Scientific advice can be requested in parallel to the EMA and the FDA, esp. in development areas of inexistent or divergent guidance or for challenging products
- A request has to be made in parallel to the two Agencies as detailed in the PSA General Principles document
- The procedure involves by default a discussion meeting between applicant, EMA and FDA (70-day procedure) as well as bilateral EMA/FDA interactions in preparation to the discussion meeting
- PSA allows EMA and FDA to discuss and potentially align regulatory requirements across the two regions; however, each Agency maintains in decision-making independence

Parallel joint scientific consultation with HTA bodies

Health Technology Assessment (HTA) is a synthesis of effectiveness, safety and cost-effectiveness evidence which informs reimbursement and pricing decisions; it is performed in the EU by nationally-based HTA bodies (HTAs or HTAbs); to be co-ordinated by the HTA co-ordination group as of Jan 2025 allowing:

- Joint scientific consultation during development
- Joint clinical assessment around or after regulatory authorisation

Parallel joint scientific consultation, a more structured interaction between EMA and HTA bodies, offers increased opportunities for mutual understanding and problem-solving and aims at optimal and robust evidence generation for different decision-makers (EMA and HTAs), thus facilitating patient access

Also 70-day procedure including trilateral (involving applicant) and bilateral (EMA and HTA only) interactions

Scientific advice for public health emergencies (PHEs)

- Provided by the Emergency Task Force (ETF)
- For declared PHEs and for pathogens with potential to cause a PHE (preparedness)
- Early contact (PHEearlyinteractions@ema.europa.eu) is encouraged, particularly during declared PHEs, for early guidance in advance of formal scientific advice
- During a declared PHE:
  - Advice on clinical aspects follows an accelerated (20-day) timetable and is free of charge
  - Co-ordinated advice on clinical trial protocols involves relevant national competent authorities where the trial is expected to be conducted
  - Flexibilities and fee waivers may extend to other (all) areas of advice (e.g. COVID-19)

Expert Panels – Pilot Scientific Advice for medical devices

Scope

- **Class III** (all types) or **Class IIb** (if active and to administer or remove a medicinal product) medical devices, **IVDs outside of scope**
- **Clinical development strategy** and proposals for **clinical investigation**
- Open to **all expert panels' clinical fields**

Main characteristics

- The pilot will take place **during 2023** aiming at full implementation after Q2 2024
- A maximum of **10 applications** with a special focus on "**orphan**", **paediatric** and **breakthrough devices** for unmet medical need
- **SME**s are encouraged to participate
- During the pilot phase, the advice is provided **free of charge** and will **not be published** due to its confidential nature

EMA to also explore scientific advice on drug-device combinations in 2023

National and simultaneous national scientific advice (SNSA)

- Scientific advice from individual National Competent Authorities (NCAs)
  - Wide scope but mainly intended for products of national interest, often from academics, commonly used to clarify clinical trial requirements
  - Although informative, not binding to the CHMP
- Simultaneous national scientific advice (SNSA)
  - Given by two NCAs (for now) in a parallel procedure
  - Wide scope similar to national and centralised (EMA/SAWP/CHMP) scientific advice but hoped to become a vehicle for consolidated pre-clinical trial application scientific advice

Please also refer to Scientific Advice on medicines for Human use in the EU medicines regulatory network (europa.eu)

Take home messages

- Scientific advice constitutes the core of regulatory support during medicine development
- The wording of questions is critical for the applicant to make the most out of a scientific advice request
- Compliance with scientific advice is predictor of authorisation application success
- Preparation is key to pre-empt technical issues with submission and for communication during the regulatory assessment; the IRIS platform is intended to be utilised eventually for all regulatory interactions with the EMA
- The scientific advice framework has been evolving: it offers qualification of novel methodologies, parallel advice with FDA and HTA, advice for public health emergencies; advice for medical devices and drug-device combinations is in development

Thank you for your attention

Further resources

- Scientific advice and protocol assistance | European Medicines Agency (europa.eu)
- EMA Guidance for Applicants seeking scientific advice and protocol assistance
- Qualification of novel methodologies for medicine development | European Medicines Agency (europa.eu)
- For ad hoc questions: scientificadvice@ema.europa.eu or, alternatively, Send a question to the European Medicines Agency | European Medicines Agency (europa.eu)

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