EMA Scientific Advice

EMA SME 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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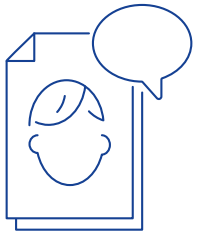
What is scientific advice?



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

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 orphan designation and its maintenance 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 (Regnström 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 to the same level as non-orphan products and big pharma applicants (Regnström et al, 2010, Hofer et al, 2015, Hofer et al, 2018)

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)

Outline

What is scientific advice

How EMA scientific advice works

Variations of the advice process

The Scientific Advice Working Party (SAWP)

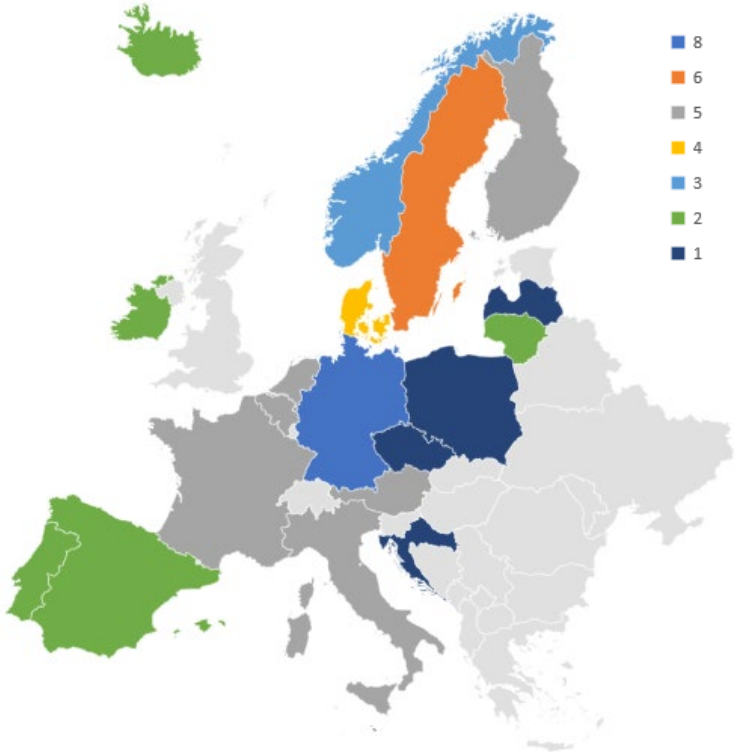
- Standing working party of the Committee for Medicinal Products for Human Use (CHMP) with the sole remit of providing scientific advice
- Meets on a monthly basis 11 times per year (no meeting in early August)
- Consists of up to 72 members and alternates nominated based on expertise needs including 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

SAWP composition and expertise (Nov 2023)

Area of expertise	Members
Clin pharmacology/trial methodology	10
Statistics	4
Modelling and Simulation	2
Non-Clinical	4
Quality	4
Vaccines/ATMP	3
Rare diseases	1
Oncology	9
Infectious Diseases	4
Neurology/Psychiatry	3
Haematology	5

Area of expertise	Members
Rheumatology/Immunology	4
Cardiology	2
GI/hepatology	2
Endocrinology/Metabolic diseases	2
Nephrology	2
Ophthalmology	1
Anaesthesiology	1
Medical Devices	1
Pulmonology	0
Geriatric medicine	1
Neonatology	1

EU Member State representation at the SAWP



SAWP referrals to committees, WPs and OEGs

Action	(To) Whom?	What?
delegates to	BWP/QWP core team	Quality
delegates to	COMP	Significant benefit
systematically involves	PDCO	Paediatric with PIP
systematically involves	CAT	ATMPs
systematically involves	PRAC	PASS
systematically involves	BSOEG	Statistics (all clinical)
systematically involves	MSOEG	M&S (all clinical)

SAWP referrals to WPs (cont.) and other groups

Action	(To) Whom?	What?
ad hoc involves	PDCO	Paediatric without PIP
ad hoc involves	NCWP	Non-clinical
ad hoc involves	MWP	Pharmacokinetics
systematically involves	GMP-IWG	GMP
systematically involves	CTCG	Qualifications of innovative or decentralised Clinical Trial designs
systematically involves	GCP-IWG	Qualifications involving Digital Health Technologies (DHTs)

How to submit a scientific advice request

Submission occurs using the online platform IRIS

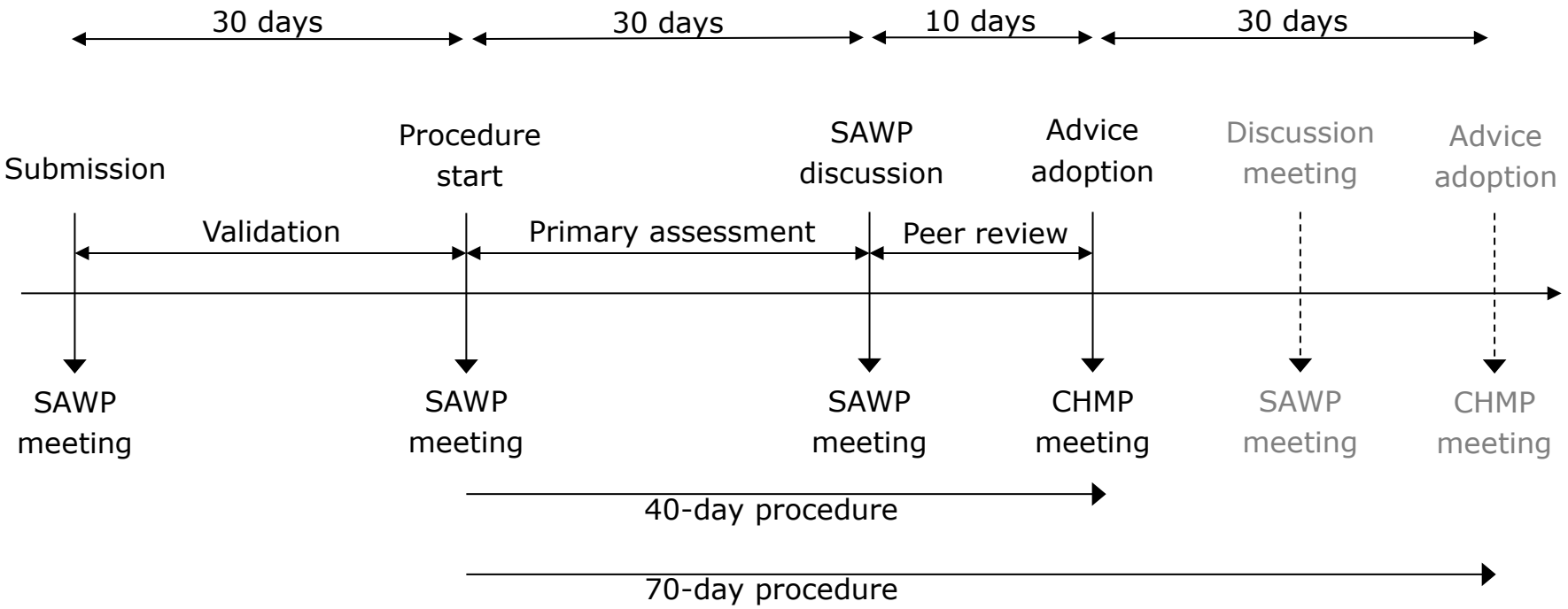
The applicant organisation, contact point, active substance and medicinal product need to be registered with the EMA (refer to the Quick interactive guide to IRIS registration process). In addition, a Research Product Identifier (RPI) needs to be requested, if not available already from prior regulatory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

For further information and training:

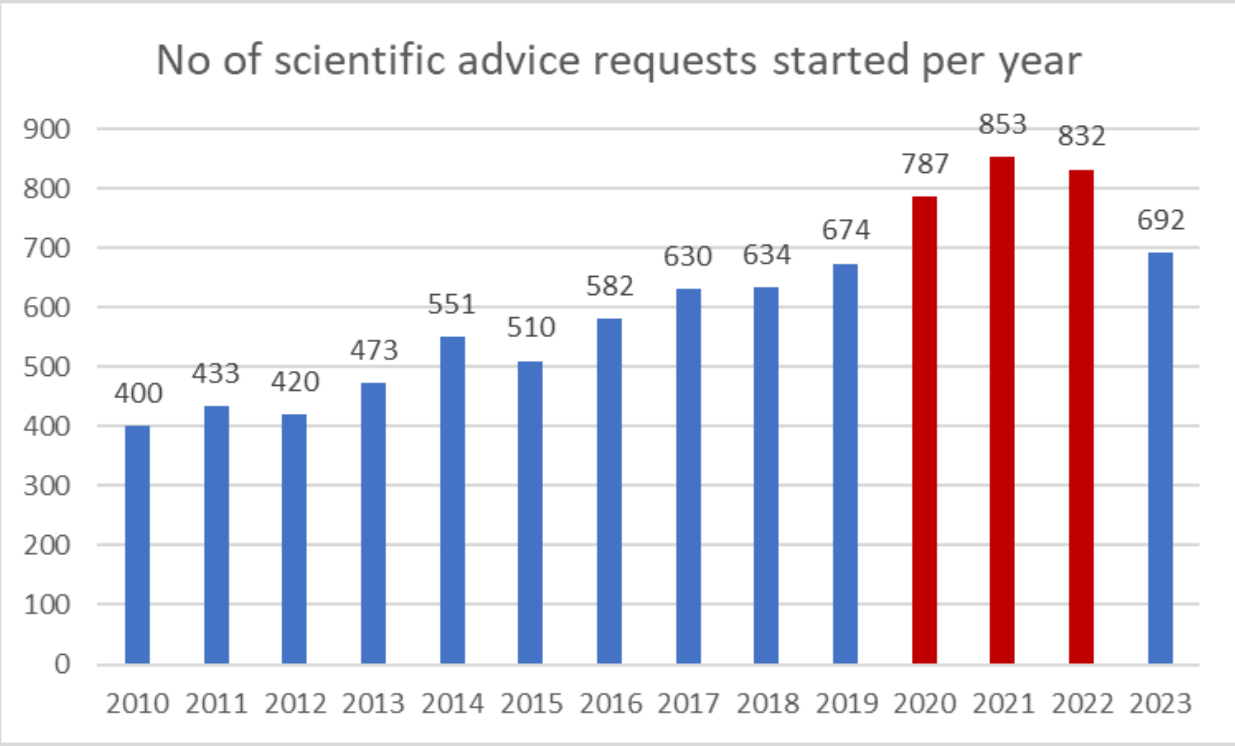
Online training: how to register for access to IRIS; what research product identifiers (RPI) are and how we use them | European Medicines Agency (europa.eu)

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 volumes



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

Outline

What is scientific advice

How EMA scientific advice works

Variations of the advice process

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 (and other) advice ahead of clinical trials

SAWP-CTCG pilot

- On suitability of clinical trial design to support CTA and MAA
- Follows the SAWP process with CTCG involvement (intra-NCA coordination between SA and CT assessors)
- Consolidated output with option for member state comments
- Will run for ~10 months (10 cases) from the 10 June 2024 launch

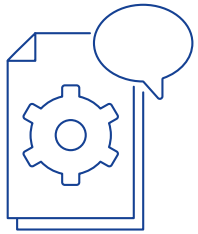
Pre-CTA advice from the CTCG pilot

- Technical and regulatory advice before the submission of a CTA
- 30-day procedure
- Applications via SNSA inbox
- RMS raises a single fee
- Interim evaluation of the pilot every 5 cases

CTA: clinical trial application, MAA: marketing authorisation application, R/CMS: reference/concerned member state, NCA: national competent authority, SA: scientific advice, CT: clinical trial, SNSA: simultaneous national scient. advice

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

PRIority MEdicine (PRIME) scheme

- Intended to foster the development of medicines with **major public health interest** and in particular from the viewpoint of **therapeutic innovation** in areas of **unmet medical need**
- Eligibility request assessed by the SAWP towards recommendation to CAT/CHMP towards granting the PRIME designation
- Reinforced scientific and regulatory advice via **early CAT/CHMP Rapporteur appointment** and **scientific advice**
- Optimised development for robust data generation in order to enable **accelerated assessment**

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)

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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