



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Scientific Evidence Generation Department

## European Medicines Agency Guidance for Applicants seeking scientific advice and protocol assistance

This guidance document addresses a number of questions that users of the scientific advice or protocol assistance procedures may have.

It provides an overview of the procedure to obtain scientific advice or protocol assistance and gives guidance to Applicants in preparing their request. This guidance document also explains the scope and nature of scientific advice and protocol assistance. It ~~will enable~~enables Applicants to submit requests which are in line with Scientific Advice Working Party (SAWP) requirements and which can be validated and evaluated quickly and efficiently.

Furthermore, Applicants ~~will be~~are guided through the different steps of the procedure and receive useful information on the preparation of a possible discussion meeting with the SAWP.

This guidance document is updated regularly to reflect new developments and include accumulated experience.

~~In particular, this version was amended to modify the submission process.~~



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## Instructions for users

To obtain information on a certain topic, simply click on the highlighted keyword. We trust that the information linked to the keyword should answer most of your queries.

If you seek further information on any of the included topics, do not hesitate to send your request to the general scientific advice inbox: [scientificadvice@ema.europa.eu](mailto:scientificadvice@ema.europa.eu) and we will deal with your query in a timely manner.

It should be highlighted that this document should be read in conjunction with the relevant legislation and guidance, including:

- ~~Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004;~~
- ~~European Parliament and Council Directive 2001/83/EC of 6 November 2001 as amended;~~
- ~~The rules governing medicinal products in the European Union, Volume 2A, Notice to Applicants;~~
- ~~Regulation (EC) 141/2000 of 16 December 1999 on orphan medicinal products;~~
- ~~Commission Regulation (EC) 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal products as an orphan medicinal product and definitions of the concept of "similar medicinal product" and "clinical superiority";~~
- ~~Council Regulation (EC) No 1905/2005 of 14 November 2005 amending Regulation (EC) No 297/95 on fees payable to the European Medicines Agency, as amended;~~
- ~~EMA public statement on fee reduction for designated for designated Orphan Medicinal Products (EMA/663496/2012);~~
- ~~EMEA/CHMP/69686/04/rev7 – Mandate, Objectives and Rules of Procedure of the scientific advice Working Party (SAWP);~~
- ~~Regulation (EC) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004;~~
- ~~Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC, & Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use.~~

## 1. What is the legal basis of scientific advice?

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".

As such, scientific advice may be requested for all medicinal products for use in humans, [as defined in Directive 2001/83 (as amended)], irrespective of the ~~medicinal products~~ eligibility of the medicinal product for the centralised procedure, on aspects of the design of studies, trials and programs to support quality, safety and efficacy of a medicinal product.

The CHMP has established the [Scientific Advice Working Party \(SAWP\)](#) as a standing working party with the ~~sole~~ remit of providing scientific advice and protocol assistance (the name given to the scientific advice procedure for products with an Orphan Designation) to Applicants.

It is the SAWP/CHMP responsibility to give scientific advice to applicants by answering ~~to~~ questions based on the documentation provided by the Applicant in the light of the current scientific knowledge.

It is not the role of the CHMP to substitute the ~~industry's~~ Applicants' responsibility in the development of their products. The work of the SAWP will be the result of collegial work from the SAWP, its experts, the different ~~EMA~~ Working Parties, ~~drafting groups~~ Drafting Groups and Operational Expert Groups, the CHMP and the Agency Secretariat with input from other Committees where relevant, such as ~~CA~~ the COMP, PDCO, ~~HMPECAT~~ and PRAC.

Scientific advice or protocol assistance received from the Agency is not legally binding with regard to any future marketing authorisation application of the product concerned, neither on the Agency/CHMP nor on the ~~applicant~~ Applicant. Nevertheless, how closely the advice provided was followed is taken into consideration during the Marketing Authorisation Application (MAA) and any deviations from the advice given need to be well justified.

If Applicants are established outside the European Economic Area (EEA), it is advisable for Applicants developing the products to nominate a contact point within the EEA to facilitate communication between the Agency and such Applicants. This contact point may be the same as the Applicant, or not.

Scientific advice received from the Agency is applicable throughout the EU. A SAWP/CHMP ~~consultations~~ scientific advice does not preclude ~~the possibility of consultations with~~ scientific advice from national competent authorities.

## 2. What is the legal basis of protocol assistance?

After having received the European Commission decision on the designation of Orphan Drug status [based on the opinion of the Committee for Orphan Medicinal Products (COMP)], the sponsor of an orphan medicinal product is entitled to request protocol assistance prior to the submission of an application for Marketing Authorisation under Article 6 of the Regulation on Orphan Medicinal Products (EC) 141/2000.

## 3. What falls under the scope of scientific advice and protocol assistance?

Scientific advice will be given by the SAWP/CHMP on questions concerning quality (manufacturing, chemical, pharmaceutical and biological testing), non-clinical (toxicological and pharmacological tests) and clinical aspects (studies in human subjects ~~in~~, either patients or healthy volunteers, including clinical ~~pharmacological~~ trials designed to determine ~~the efficacy~~ human pharmacology (PK/PD), and ~~exploratory or confirmatory~~ safety ~~of the product~~ and efficacy studies, for pre- or post-authorisation activities including risk-management programmes). Scientific advice may also be given on issues relating to interpretation and implementation of (draft) EU and ICH guidelines.

Regardless of the authorisation status, the question(s) posed to the SAWP/CHMP by the Applicant should address scientific issues and may relate to the following:

- Any quality/manufacturing aspects e.g., characterisation, specification, quality by design, comparability
- Any non-clinical development aspects e.g., toxicology, pharmacology, choice of animal model
- Any clinical study design aspects e.g., population, stratification factors, dose regimen, comparator including external control and real-world evidence, duration, cross-over, endpoints including digital endpoints, Patient Reported Outcomes (PROs) or other Clinical Outcome Assessment (COA) measures and use of biomarkers as surrogate endpoints, safety monitoring plan, and for any type of clinical study (e.g. first-in-human, bioequivalence studies, dose-finding, development in special populations, clinical pharmacology, pivotal trials, post-approval trials and registry-based studies)

- Any methodological issues (e.g., statistical analysis plan, type I error control, adaptive designs, Bayesian approaches, extrapolation strategy, modelling and simulation)
- Overall development strategy (e.g., adequacy of development plan to support marketing authorisation application - except in a paediatric population (refer to Question 6) -, conditional marketing authorisation or authorisation under exceptional circumstances, substitution of non-clinical/clinical trials by literature or real-world evidence, bridging strategy to support applications relying on a reference medicinal product, safety database, risk management plan).

Scientific advice is prospective in nature. It allows input on developments, which can be amended after SAWP/CHMP advice. Scientific advice focuses on development strategies ~~rather than~~ and abstains from pre-evaluation of already available data/results to support a Marketing Authorisation application.

~~For advice or procedural guidance relating to~~ Scientific advice is product- and indication-specific. Requests not meeting both these criteria will generally not be accepted as a single advice submission, but they will trigger separate requests for each indication or product concerned. However, in case of closely developments in related indications, a single briefing package can be used to support both (all) applications (see also "broad advice" further below; for experimental combined use of multiple products see also Question 11).

The SAWP/CHMP also offers advice to support the qualification of innovative methods for a specific intended use in the context of research and development of pharmaceuticals, such as biomarkers and qualification of novel methodologies for drug development. For advice or procedural guidance of this type, Applicants are ~~also~~ advised to consult ~~the~~ [the Qualification of novel methodologies for drug development: guidance to applicants](#).

According to Regulation (EC) No 726/2004, in addition to the above-mentioned provisions, the Agency /SAWP may also deal with the following aspects:

- ~~Broader and more general advice for specific types of medicinal products or therapies, in collaboration with the relevant Working Parties. "Specific types of medicinal, i.e., affecting multiple products and therapies" may refer e.g. to a class of medicinal products, the use of scales in a therapeutic indication or the use of new expression systems. An Applicant may also request advice on product-specific scientific questions and/or include topics, at earlier time points of a development program, which may cover several/or indications. These requests could pertain to:~~
  - ~~– basket trials investigating multiple indications for the same product~~
  - ~~– experimental use of multiple medicines in combination or in parallel in a single umbrella or platform trial; of note, no product-specific questions beyond the platform trial are acceptable in such broad advice (see also Question 11)~~
  - ~~– on, typically but not exclusively, quality changes (e.g., changes to manufacturing facilities) affecting multiple products or multiple indications of the same product~~

For a broad advice and depending on the ~~Agency strongly recommends having complexity of the topic, the Applicant could consider requesting a~~ scientific advice preparatory ~~meetings~~meeting.

- Advice about the justification on whether a specific medicinal product being developed for a specific therapeutic indication falls within one of the categories set out in Article 2 and fulfils the condition laid down in Article 4(1)(c) of Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004.

- ~~Scientific advice requests on acceptability~~[Advice on adequacy](#) of the development programme for conditional marketing authorisation, which are defined in Article 14(7) of Regulation (EC) No 726/2004.
- Advice about the justification for applying for a marketing authorisation under exceptional circumstances (Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to article 14(8) of Regulation (EC) No 726/2004; EMA/357981/2005-), ~~and the adequacy of the supportive development programme.~~
- ~~Scientific advice requests on acceptability of the development programme for marketing authorisation application under exceptional circumstances, which are defined in article 14(8) of Regulation (EC) No 726/2004.~~
- ~~Scientific advice requests~~[Advice on the design of any other post-authorisation efficacy or safety study or any other aspect of post-authorisation evidence generation.](#)
- [Advice](#) on the design of trials to assess safety and efficacy in a new indication expected to bring significant clinical benefit compared to existing therapies as defined in Article 14(11) of Regulation (EC) No 726/2004 or Article 10(1) fourth subparagraph of Directive 2001/83/EC, as amended.
- ~~Scientific advice requests~~[Advice](#) on the design of trials to assess safety and efficacy in a new indication for a well-established substance in accordance with Article 10(5) of Directive 2001/83/EC as amended.
- ~~Scientific advice requests for medicinal products intended to be marketed exclusively outside the Community, in the context of WHO collaboration as defined in Article 58(2) of Regulation (EC) No 726/2004 (see also Agency Guidance).~~
- ~~Scientific advice requests on scientific aspects of a paediatric development.~~
- ~~Scientific advice~~[Advice](#) on the proposed safety and efficacy data requirements or the approach to addressing relevant criteria for an application to change the classification for the supply of a medicinal product from subject to a medical prescription to not subject to a medical prescription. ~~See European Commission on "A Guideline on changing the classification for the supply of a medicinal product for human use". Refer also to "A Guideline on changing the classification for the supply of a medicinal product for human use".~~
- ~~The use of modelling and simulation for specific aspects of drug development.~~
- ~~Advice for medicinal products intended to be marketed exclusively outside the Community, in the context of WHO collaboration as defined in Article 58(2) of Regulation (EC) No 726/2004 (see also Medicines for Use outside the European Union).~~
- ~~Advice on specific aspects of a paediatric development without seeking pre-assessment of a Paediatric Investigation Plan (PIP) nor confirmation of the adequacy of plans to support a paediatric indication, also noting that any impact on key elements of an existing PIP would need to be subject to a modification procedure at PDCO (please also refer to Question 6 below).~~
- Scientific advice on the ancillary medicinal component of a medical device, provided the request for scientific advice is solely focusing on the development needed to enable the Notified Body to submit the results of the test/trials on the application needed for EMA to be in the position to provide a scientific opinion (perform its Benefit/Risk assessment) as per document EMA/CHMP/578661/2010 "European Medicines Agency recommendation on the procedural aspects and dossier requirements for the consultation to the European Medicines Agency by a notified body

on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device or active implantable medical device”.

- For emerging therapies and borderline products with uncertainties [on product classification](#), Applicants are advised to seek Regulatory advice on the eligibility to the European Medicines Agency procedures as Medicinal Products according to Art. 1 and 2 of Directive 2001/83 as amended.

The following remain **outside of the scope of the scientific advice procedure**:

- ~~Compassionate use~~[Compassionate use](#) as defined in Article 83 of Regulation (EC) No 726/2004.
- [Recommendations on classification of ATMPs, as set out in Article 17 of Regulation \(EC\) No 1394/2007. See also Advanced Therapy classification](#)
- [Questions directly related to eligibility to EMA PRiority Medicines \(PRIME\) scheme, for which information on how to access this scheme can be found in the “How to apply” section.](#)
- Agency advice prior to submission for qualification of a request for an accelerated assessment procedure. Guideline on the procedure for ~~Accelerated assessment~~[Accelerated assessment](#) pursuant to Article 14(9) of Regulation (EC) No 726/2004 (EMA/419127/05).
- ~~Paediatric Investigation Plans~~[PIPs](#) as defined in the Regulation (EC) No 1901/2006 on medicinal products for paediatric use, as amended. ~~Advice; explicit or implicit questions on waivers, deferrals or, questions on adequacy of studies and proposed measures to support paediatric indications, changes to key elements of an agreed Paediatric Investigation Plan which would require a PIP modification, e.g., replacement of PIP measures by new ones, or other~~ specific regulatory issues that are the exclusive mandate of the Paediatric Committee. ~~(please also refer to Question 6 below).~~
- ~~Regulatory~~[Purely legal, regulatory and non-scientific](#) aspects ~~which are handled by the Agency Secretariat~~ (e.g. ~~discussion, formal requirements~~ regarding ~~the~~ legal basis for submission, format of marketing authorisation application and Common Technical Document [requirements, file formats, acceptable language of documentation to be submitted](#) etc.). ~~Regulatory and administrative~~[Such](#) questions can be answered by the Agency ~~Secretariat~~[secretariat](#) directly during a [scientific advice preparatory meeting](#), if pre-notified, ~~(via inclusion in the ‘Submission Details’ field in the IRIS portal section), or in writing post-meeting, or at later meetings with the Agency-~~ ~~(e.g., at a pre-submission meeting prior to an MAA).~~

## Potential Questions

~~Whatever the authorisation phase is (pre or post), the question(s) posed to the SAWP/CHMP by the Applicant should address scientific issues and may relate to the following:~~

- ~~Any quality aspects (e.g. characterisation, specification, quality by design, comparability)~~
- ~~Any non-clinical aspects (e.g. toxicology, pharmacology, choice of animal model)~~
- ~~Any clinical aspects (e.g. first in man, bioequivalence studies, dose finding, development in special populations, clinical pharmacology, pivotal trials, post approval trials)~~
- ~~Any methodological issues (e.g. use of biomarkers as surrogate endpoints, modelling and simulation, statistical analysis plan, adaptive designs, Bayesian approach, extrapolation strategy)~~
- ~~Overall development strategy (e.g. development strategy to support marketing authorisation application, conditional marketing authorisation or authorisation under exceptional circumstances,~~



~~substitution of non-clinical/clinical trials by literature, bridging strategy, safety database, risk management plans).~~

- Pre-assessment of completed data packages or of completed parts of development for the sole purpose of confirming the adequacy of the data to initiate clinical trials (adequacy of data to support clinical trial approval is in the remit of National Competent Authorities and Ethics Committees) or a future marketing authorisation (e.g., adequacy of completed quality or non-clinical development package; adequacy of pivotal clinical trial data for authorisation decisions, sufficiency of already generated data to support specific labelling claims).

Similarly, questions on the design of ongoing clinical studies should only be asked under the assumption that study design changes are still possible and potential recommended amendments would not impact on the integrity of the study. Such questions should be duly justified and the impact of any potential protocol amendments on study integrity should be considered and described in the Applicant's position. Acceptability of study design elements that can no longer be changed is a matter of assessment at the time of marketing authorisation application.

## 4. Protocol assistance particular issues

**Specifically for protocol assistance**, the questions and proposed development plan ~~should~~must be within the scope of the designated orphan indication to avail of the fee reductions.

~~The procedure for provision of protocol assistance will follow mainly the procedure for provision of scientific advice with involvement of the COMP and associated Secretariat.~~

Similar to the scientific advice request, the request for protocol assistance should contain prospective questions concerning quality, ~~non-clinical and clinical aspects (studies in human subjects in either patients or healthy volunteers, including clinical pharmacological trials designed to determine the efficacy and safety of the product for pre or post authorisation activities)~~non-clinical and clinical aspects relating to the proposed future development of the orphan medicinal product within the scope of the designated indication.

~~Also~~Moreover, questions related to the demonstration of one of the designation criteria (significant benefit) for the maintenance of Orphan Status may be raised.

~~Regulatory aspects should be the matter of a separate request. Regulatory and administrative questions can be answered by the Agency Secretariat directly during a scientific advice preparatory meeting if pre-notified, or in writing, or at later meetings with the Agency.~~

The procedure for provision of protocol assistance will follow mainly the procedure for provision of scientific advice, with involvement of the COMP on significant benefit questions.

Three main types of specific questions are anticipated. Two are related to the criteria for marketing Authorisation and one is related to the demonstration of one of the designation criteria, i.e. ~~..~~ significant benefit, for the maintenance of Orphan Status:

### Related to the criteria for marketing Authorisation

- Request concerning the proposed development plan of medicinal products for rare conditions (where ~~..~~ by definition ~~..~~ the population is small) to demonstrate efficacy and safety.
- Request concerning study design to demonstrate *clinical superiority* over a similar orphan product authorised for the same indication based on EC 141/2000, Art. 8.3(c) and EC 847/2000, Art. 3.3(d) - in order to justify a derogation from Market Exclusivity:



- [...] the second Applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior. ([EC 141/2000](#), 8.3(c))
- Clinically superior means that a medicinal product is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more ways [...] ([EC 847/2000](#), Art. 3.3(d))

This is necessary when a “similar” orphan medicinal product (as defined in Article 3 of Regulation (EC) [No 847/2000](#)) has received marketing Authorisation and will likely still ~~attract~~ be entitled to Market Exclusivity for the same therapeutic indication at the time of prospective MAA of the investigational medicinal product which itself may have orphan status or not.

### **Related to the criteria for designation of Orphan Drug status (*Significant benefit criterion*)**

When another satisfactory method exists in the Community (including authorised medicinal products) for the same orphan indication, the designation is based, among others, on the criterion of significant benefit.

Significant benefit means (Article 3.2 of Regulation (EC) No 847/2000) “a clinically relevant advantage or a major contribution to patient care”.

An assumption of significant benefit at the time of designation has to be demonstrated at the time of marketing authorisation (Article 5.12 of Regulation EC No 141/2000 states “if it is established before the market authorisation is granted that the criteria laid down in Article 3 (criteria for designation) are no longer met ... a designated orphan medicinal product shall be removed from the Community Register of Orphan Medicinal Products”. See also the ~~Agency guidance on Orphan Medicinal products~~ [Agency guidance on Orphan Medicinal products](#).

## **5. At what phase of product development can an Applicant request scientific advice ~~or~~ / protocol assistance?**

Scientific advice or protocol assistance can be requested during the initial development of the medicinal product (before submission of the marketing authorisation application) but also during the post-~~authorisation phase~~ authorisation phase towards further development. It is discouraged to request scientific advice or protocol assistance close to the submission of the marketing authorisation application and in relation to the indication(s) pursued in an ongoing marketing authorisation application, as initial development must be complete at this point.

Scientific advice or protocol assistance requested during the post-~~authorisation phase~~ are of a particular product is generally related but not ~~exclusively~~ restricted to the following cases:

- A new formulation ~~or~~ dosage form or route of administration
- A new or a change of manufacturing process or other major quality/manufacturing change
- An extension of indication
- ~~A new or a change of manufacturing process~~
- ~~Post-~~authorisation~~ studies~~
- Post, e.g., in the context of the design of studies to address conditions of a marketing authorisation-specific obligations/follow-up measures (in agreement with the CHMP Rapporteur)-

## 6. Can scientific advice/protocol assistance be requested on paediatric development?

The Paediatric Regulation provides that any legal or natural person developing a medicine intended for paediatric use may request scientific advice from the EMA. Advice ~~including that only includes~~ questions on paediatric development ~~only are~~is free of charge.

~~Applicants may choose to request scientific advice first, to help with the preparation of specific aspects of a paediatric investigation plan (PIP), or to prepare and/or submit a PIP directly to the EMA Paediatric Medicines Office and follow it up with a request for scientific advice on, for example, combined adult and paediatric developments in light of the PIP requirements and PDCO discussions. For scientific guidance on the entire PIP development and submission, pre-submission discussions, when required, should be planned with the EMA Office of Paediatric Medicines (in line with published guidance) rather than requested through scientific advice/protocol assistance of the SAWP/CHMP.~~

~~The procedure for requesting scientific advice/protocol assistance should be followed as indicated. It is important that the Applicant completes the relevant paediatric elements within the IRIS submission.~~

~~Questions posed by the Applicant seeking advice can address all issues of the pharmaceutical, non-clinical and clinical development of the product and the data required for a marketing authorisation Application for the paediatric indication. Advice on waivers, or deferrals or specific regulatory issues that are the exclusive mandate of the Paediatric Committee are out of scope of the scientific advice procedure.~~

~~Applicants may request scientific advice on, e.g., design elements of a specific study included in a PIP. Applicants can also request scientific advice on combined adult and paediatric developments in light of specific PIP requirements and PDCO discussions. As it is the remit of the PDCO to agree the overall measures to generate evidence to support a paediatric indication while scientific advice focuses on more specific design elements, it is generally advisable that the applicant has agreed a PIP before pursuing scientific advice on their paediatric development. Advice on specific aspects of such development in advance of any agreed PIP should not be understood as implicit principle agreement that the programme is appropriate to meet the requirements from an overall paediatric development perspective nor as replacement for a timely submission of a PIP.~~

~~Consequently, **the following questions fall under the remit of the PDCO and should not be subject of scientific advice/protocol assistance of the SAWP/CHMP:**~~

- ~~• Questions encompassing the entire paediatric development and in preparation of a PIP submission, including appropriateness of potential target populations and overall data requirements to support a paediatric indication~~
- ~~• Quality development of paediatric formulations~~
- ~~• Nonclinical studies to be conducted to support the use in paediatric patients~~
- ~~• Questions on waivers, deferrals and associated regulatory issues~~
- ~~• Changes to studies or key elements of an agreed PIP which would require a formal amendment of an existing PIP.~~

~~In such cases, applicants should contact the EMA Paediatric office for pre-submission guidance or submit the PIP or modification for assessment by the PDCO.~~

~~It is important that the Applicant completes the relevant paediatric fields during the IRIS submission.~~

Furthermore, submitting a scientific advice/protocol assistance request in parallel to a PIP submission/amendment review is generally discouraged, except if specifically proposed by PDCO in the PIP request for modification.

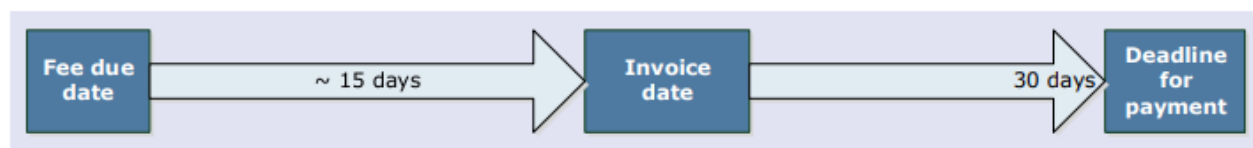
For rRequests of scientific advice/protocol assistance on paediatric ~~development plan~~developments, where a PIP ~~has been agreed or a PIP~~ review is ongoing, it is ~~recommended~~required to include the latest ~~Decision or the latest~~ version of the Summary Report, ~~respectively, in IRIS in IRIS~~ and a comparative table in the briefing document, outlining the proposed changes to the paediatric development programme as compared to the data previously discussed by the PDCO, where relevant.  
**Members**

When relevant, members of the ~~Paediatric Committee~~PDCO will be consulted and/or invited by SAWP to participate as individual experts during the scientific advice/protocol assistance procedure. The EMA secretariat ensures that relevant information is exchanged and that views are aligned between PDCO and SAWP/CHMP.

## 7. What are the fees for scientific advice and when should they be paid?

Scientific advice procedures are not paid in advance. Instead, the Agency will issue an invoice ~~on the date of the~~approximately 15 days following notification of the administrative validation to the Applicant and fees will be payable within 4530 calendar days ~~of the date of the notification. For details please refer to the Explanatory note on fees payable to the European Medicines Agency from the invoice date.~~  
In summary, the procedure shown in Figure 1 applies.

**Figure 1.** Procedure for fee determination and payment



The following definitions shall apply for the determination of fees for scientific advice requests:

### Disciplines

- Quality development: ~~chemical~~Chemical, pharmaceutical and biological testing.
- ~~Safety~~Non-clinical development ~~(non-clinical): toxicological; Toxicological~~ and pharmacological in vitro tests and animal studies.
- Clinical development: studies in human subjects ~~in whether patients or non-patient volunteers;~~ including clinical ~~pharmacological~~ trials designed to determine the human pharmacology (PK/PD), exploratory and confirmatory safety and efficacy and safety studies or approaches (e.g., use of the product literature/real-world-evidence or modelling and simulation) to substitute clinical testing.
- Initial request: first request for scientific advice or protocol assistance introduced in relation to the submission of an application in the pre- or post-authorisation phase.
- Follow up to initial request: any subsequent request falling within the same therapeutic indication and discipline area(s) as the initial request (area means referring to quality, safety and/or clinical development ~~including pharmacovigilance/risk management aspects~~).

Ranges and classification of fees for scientific advice relating to medicinal products for human use:

### 1. Initial request

### Fee level III

For initial requests on:

- quality ~~and safety and~~, non-clinical and clinical development, or
- quality and clinical development, or
- safety non-clinical and clinical development
- qualification advice

### Fee level II

For initial requests on:

- clinical development, or
- quality and safety non-clinical development, or
- quality and bioequivalence studies for generic medicinal products

### Fee level I

For initial requests on:

- quality development, or
- safety non-clinical development, or
- bioequivalence studies for generic medicinal products

## 2. Follow-up to the initial request

### Fee level III

For follow-up on:

- quality ~~and safety~~, non-clinical and clinical development, or
- quality and clinical development, or
- safety non-clinical and clinical development
- qualification advice

### Fee level II

For follow-up on:

- clinical development, or
- quality and safety non-clinical development, or
- quality and bioequivalence studies for generic medicinal products

### Fee level I

For follow-up on:

- quality development, or
- safety non-clinical development
- bioequivalence studies for generic medicinal products

For further details please refer to the [Explanatory note on fees payable to the European Medicines Agency](#).

## 8. How do I request a fee reduction for protocol assistance?

~~It is no longer necessary to submit a separate fee reduction request~~To be eligible for medicinal products with an Orphan orphan fee incentives, all of the following conditions must be met at the fee due date (date of notification of administrative validation):

- A decision of the European Commission must be in place (product registered in the Community Register)
- The Applicant for Protocol Assistance and the Sponsor of the designation. The fee reduction entitlement will be checked internally. Applicants should ensure that all necessary information relating to must be the same entity.
- The indication for which advice is sought must match the orphan designation [indication](#).

Please note that the positive COMP opinion on orphan designation is ~~provided~~not sufficient for eligibility to the orphan fee reduction.

The aforementioned conditions are checked at the time of submission and a fee reduction is automatically applied when the conditions are met.

## 9. How do I request a fee reduction for small and medium-sized enterprises (SME)?

Pursuant to Article 70.2 of Regulation (EC) No 726/2004 of 31 March 2004, SMEs are eligible for fee reductions, fee deferrals and conditional fee exemptions in accordance with Regulation (EC) No 2049/2005 of 15 December 2005. This includes fee reductions for scientific advice, pre- and post-authorisation inspections, scientific services, and a full fee waiver for administrative services (with the exception of parallel distribution). There is also the possibility to defer payment of the fees payable for the application for marketing authorisation and pre-authorisation inspections, and receive a conditional fee exemption where scientific advice has been given and the application for marketing authorisation is not successful (i.e. ~~it~~ does not result in the grant of a marketing authorisation).

It should be noted that fee reductions can only be considered once the Applicant has been assigned SME status by the Agency. ~~It is no longer necessary to submit a separate fee reduction request for SMEs.~~ The fee reduction entitlement will be checked internally at the time of submission and applied automatically Applicants should ensure that all necessary information relating to the SME status is provided at the time of submission to avoid unnecessary charges.

Where an SME Applicant could, in respect of the same fee, also benefit from other reductions provided for in Community legislation (e.g. ~~it~~ Orphan Medicinal Product legislation), the provisions which are most favourable to the Applicant will apply. Cumulative fee reductions for a given fee and a given Applicant will not be accepted.

~~See the EMA website for~~For further information on the level of fee reductions available to SME Applicants and how to apply for SME status or contact the SME office: [smeoffice@ema.europa.eu](mailto:smeoffice@ema.europa.eu)

~~The User guide for micro, small and medium-sized enterprises is also recommended for further information.~~

please refer to the [Explanatory note on fees payable to the European Medicines Agency, available at this webpage](#).

[For information on how to apply for SME status please refer to the relevant webpage: Support to SMEs | European Medicines Agency \(europa.eu\).](#)

## 10. How does the regulation on Advanced Therapies impact on the scientific advice/protocol assistance procedure?

Regulation (EC) No 1394/2007 on advanced therapy medicinal products lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products (gene therapy, somatic cell therapy and tissue engineering).

For detailed information on the regulation please see the EMA website on advanced therapies.

As a result of this legislation the Agency has introduced changes in the SA/PA procedure to reflect the needs of Applicants dealing with Advanced Therapies, these include:

- A 65% fee waiver for the scientific advice procedure for a product in this field
- Contribution of the members of the Committee for Advanced Therapies in the discussion of the scientific advice, before finalising the advice.

~~No special request for fee reduction has to be submitted.~~ The fee reduction will be automatically be applied ~~during the following scientific~~ validation of the ~~final~~ request ~~by the assigned scientific officer~~, provided that the request falls within the legislative scope of the reduction.

~~The fee reduction will be reflected in the invoice generated after the start of the procedure.~~

For Advanced Therapies Medicinal Products (ATMPs) with uncertainties regarding their status, Applicants are advised to seek a scientific recommendation on the classification of ATMPs by the Committee for Advanced Therapies (CAT) according to Article 17 of Regulation (EC) No 1394/2007.

The purpose of this procedure is to allow Applicants to clarify, in case of doubt, the classification whether a given product based on genes, cells or tissues meets the scientific criteria which define ATMPs, in order to address, as early as possible, questions of borderline with other areas such as cosmetics or medical devices, which may arise as science develops. However, this procedure does not replace CHMP scientific advice.

## 11. How do I apply for scientific advice/protocol assistance and how will my application be validated?

The Applicant submits an application including a request and draft briefing document and supporting documentation (briefing package) via the [IRIS](#) platform ~~for feedback See question 12.~~

~~The Applicant submits an **Electronic Final Package (final request)** for validation which has been updated following EMA feedback. See question 13.~~

If a scientific advice or protocol assistance preparatory meeting is requested when applying, the submission deadline is approximately 8 weeks before the intended start of the procedure. If no preparatory meeting is requested the deadline for submission is approximately 4 weeks before the intended start of the procedure. The dates of forthcoming SAWP meetings and deadlines for scientific advice or protocol assistance submissions are available on the scientific advice website.

The Briefing document is the most critical part of the briefing package. The review of the scientific advice or protocol assistance request by the SAWP will primarily be based on the questions and Applicant's positions presented by the Applicant in the Briefing document. It is **mandatory** to use the [CHMP scientific advice/protocol assistance briefing document template](#). The annotated template

provides detailed guidance on how to compile the scientific advice/protocol assistance Briefing document, annexes and references. Please see the EMA scientific advice website for the latest versions of the Briefing document template.

After receipt of the application, the request for scientific advice or protocol assistance is validated by the appointed scientific advice officer within the Agency Secretariat with regard to structure and content of request including the scope of the questions. On the basis of EMA validation comments and requests for changes to the application and the submitted documentation, the Applicant modifies the application on the IRIS platform and submits an **updated briefing package** for formal validation, unless no validation issues are raised.

Following receipt of the updated briefing package and any necessary modifications to the application on IRIS, the request for scientific advice or protocol assistance is formally validated by the Agency Secretariat with regard to:

- a) Update of the request within the required deadline and
- b) Structure and content of request including the scope of the questions in line with the validation issues raised

If one of these criteria is not according to the requirements set out in this guidance, the request will not be considered valid and shall be postponed or withdrawn.

Once all validation issues have been resolved, a **final briefing package** is submitted by the applicant making any potential pending minor modifications to the Briefing document and correcting potential mistakes in the application in IRIS.

For more details on the validation steps and timeline, please also refer to Question 18.

Please note that in order to submit an application via ~~IRIS~~IRIS a research product identifier (RPI) is required to track medicines and methodologies through pre-authorisation procedures.

Companies and individuals that approach EMA for the first time with a new product will need to request a new RPI via ~~IRIS. However, if~~IRIS. Additional RPIs may be needed to (create and/or) assign to a scientific advice request for other products used experimentally (i.e., outside their approved use, if any) in combination with the product which is the object of the advice. Questions specific to such combination partners are not allowed and they would trigger additional separate applications. In case the new RPI is not being requested for a single medicinal product (including fixed-dose combinations) but for multiple products, a technology, a methodology or other topic for discussion, the request should be sent directly to [scientificadvice@ema.europa.eu](mailto:scientificadvice@ema.europa.eu).

~~See below for further details.~~The same process applies for requests for follow-up advice-, unless the RPI has already been assigned via an initial request having been made via IRIS.

## **12. What is the structure/content of the briefing package for scientific advice or protocol assistance?**

The briefing package should be presented as follows:

- i. Briefing document including the Questions and Applicant's positions (in Word format)

The initial briefing document must be clearly marked as DRAFT in the filename and any updated version clearly marked as UPDATED, while only the agreed, finally submitted briefing document should be marked as FINAL in the filename. The UPDATED briefing document should be presented in both a clean and a track-changes version highlighting changes from the DRAFT. Both DRAFT and FINAL should only be presented as clean files. If no further minor



changed are needed in the UPDATED briefing document, a version marked as FINAL may not need to be submitted; the initial DRAFT, if acceptable, or the clean UPDATED version will serve as the final briefing document.

ii. Annexes (in Word or pdf format)

iii. References (in pdf format)

Annexes and References should be submitted in respective zip folders. In the less common case that these also require modification, the updated zip folder(s) should be clearly marked as FINAL.

**The briefing document should never be zipped (either on its own or together with other documents).**

## **~~12. What is the draft briefing document and what are the timelines for notification of a scientific advice/protocol assistance procedure?~~**

~~The Agency Secretariat should be formally notified of the intent to submit a scientific advice or protocol assistance request via the IRIS platform.~~

~~The draft briefing document should be presented as follows:~~

### **~~Briefing document including the Questions and Applicant's positions~~**

~~The Briefing document is the most important section of the request. The review of the scientific advice or protocol assistance request by the SAWP will primarily be based on the questions and Applicant's positions presented by the applicant in the briefing document. It is highly recommended to use the CHMP scientific advice/protocol assistance briefing document template. The annotated template provides detailed guidance on how to compile the scientific advice/protocol assistance assistance briefing document, annexes and references.~~

~~Please see the EMA scientific advice website for the latest versions of the Briefing document template.~~

~~If a scientific advice or protocol assistance preparatory meeting is requested when applying, the deadline is approximately 8 weeks before the intended start of the procedure. If no preparatory meeting is requested the deadline for submission is approximately 4 weeks before the intended start of the procedure.~~

~~The dates of forthcoming SAWP meetings and deadlines for scientific advice or protocol assistance submissions are available on the scientific advice website.~~

## **~~13. What is the structure/content of the electronic final package for scientific advice or protocol assistance?~~**

~~The package should be presented as follows:~~

### **~~i) Updated briefing document including the Questions and Applicant's positions~~**

~~The Briefing document is the most important section of the request. The review of the scientific advice or protocol assistance request by the SAWP will primarily be based on the questions and Applicant's positions presented by the applicant in the briefing document. It is highly recommended to use the CHMP scientific advice/protocol assistance briefing document template. The annotated template provides detailed guidance on how to compile the scientific advice/protocol assistance assistance briefing document, annexes and references.~~

Please see the [EMA scientific advice website](#) for the latest versions of the Briefing document template

**ii) Annexes**

**iii) References**

## **~~14. How and to whom shall I send my electronic final package for scientific advice or protocol assistance?~~**

### **~~Submitting the electronic final package~~**

~~In either case with or without the preparatory meeting, the applicant revises the draft briefing document as needed and resubmits the electronic final package (referred to as final briefing document in the published submission deadlines) which will be validated by the scientific advice officer.~~

~~The briefing document including the question(s)/Applicant's position(s) should be uploaded in IRIS in these final sets in MS Word format; a PDF version can also be submitted together with the Annexes and References. Alternatively, Annexes and References can be either MS Word or PDF documents.~~

~~Prompt submission of the final package will enable the Coordinators to review the information with sufficient time to prepare the Coordinators' first reports. A delay in submission of the package could result in a delay of the procedure by one month.~~

## **13. What is the role of the scientific advice Working Party (SAWP)?**

The SAWP is a permanent working party of the CHMP charged with drafting scientific advice, and protocol assistance for orphan medicinal products.

The SAWP is a multidisciplinary expert group and includes the chairperson and up to 36 members and their alternates, among which 1 vice-chairperson and at least 1 and not more than 3 members from each of the other EMA scientific committees, specifically the COMP, PDCO, CAT and PRAC.

The SAWP co-ordinates the provision of scientific advice and protocol assistance and brings forward to the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Orphan Medicinal Products (COMP) an integrated view as regards quality, non-clinical, clinical safety and efficacy, relating to the development of medicinal products and orphan medicinal products, and as regards significant benefit relating to orphan medicinal products.

In addition to its own expertise, the SAWP involves appropriate expertise (internal or external experts, Committees, Working Parties or Ad Hoc groups) whenever necessary, in particular in the provision of advice on the demonstration of significant benefit for orphan designation purposes (COMP), on product development for children (PDCO), on the development of Advanced therapies (CAT) and on the design of (non-interventional) post-authorisation safety studies (PASS or NI PASS) or the qualification of registries (PRAC).

The SAWP meets 11 times per year at the Agency for a 4-day meeting generally set 2 weeks before the CHMP (Dates of forthcoming meetings are published on the EMA website). The meeting is generally organised as follows: the first day is allocated for the SAWP plenary meeting on discussion of 1<sup>st</sup> reports and the following days include both plenary discussions and Discussion meetings which are run in parallel.

For further details, please refer to the Mandate, Objectives and Rules of Procedure of the scientific advice working party.

## ~~15.~~ **14. What is the role of the SAWP Coordinators?**

A "scientific advice team" is created by the Coordinators, the Agency and additional experts nominated by SAWP members. A network of internal and external experts ensures that the adequate experts are participating in the scientific advice or protocol assistance procedure.

The Coordinators are responsible for providing reports in response to the scientific advice or protocol assistance requests taking into account the [timetable](#) for evaluation of such requests. These reports are considered as working documents only and will not be released to Applicants. If necessary, the Coordinators may ask the applicant for any additional documents or clarifications.

The Coordinators will compile comments from the SAWP, the COMP (for protocol assistance), the CAT (for requests on advanced therapy medicinal products), the [other relevant EMA Working Parties](#) ~~and~~, the CHMP and their experts.

Should a [Discussion meeting](#) be decided upon with the Applicant, the Coordinators will draft the list of issues. The Discussion meeting will be chaired by one of the two Coordinators.

Experts must declare their interests before being involved in the scientific advice or protocol assistance procedures. Conflicts of interest declared by experts will be handled in accordance with the Agency ~~Policy on the Handling of declared Interests for Agency scientific Committees members and experts.~~ [Policy on the Handling of declared Interests for Agency scientific Committees members and experts.](#) All experts are bound by a confidentiality agreement.

## ~~16.~~ **15. What is the procedure for appointment of Coordinators?**

Subsequently to the submission of the application, two SAWP members will be appointed as Coordinators for the procedure. For protocol assistance, if the request includes issues relating to demonstration of significant a COMP representative to the SAWP will be involved.

In order to ensure a fair distribution of the workload, appointments of Coordinators are based on availability of appropriate expertise and equal opportunity. Preferences regarding Coordinatorship expressed by Applicants cannot be taken into consideration.

To be appointed as Coordinators, SAWP members provide the Agency Secretariat with a list of their preferred choices of products prior to the start of procedure. The timing for nomination is the same irrespective of preparatory meeting or not.

For centralised applications, the appointment of Coordinators is decided independently from any previous appointment for scientific advice or protocol assistance Coordinatorship. Also the appointment of scientific advice or protocol assistance Coordinators is decided independently from any previous appointment of Coordinators for centralised applications.

Following the appointment of Coordinators at the SAWP meeting, the applicant will receive a notification indicating the names of the appointed Coordinators and the responsible Agency scientific officer.

## ~~17.~~ **16. What is the role of the Agency scientific officer/ Agency Secretariat?**

The Agency **scientific officer** is the contact person for the ~~applicant~~ [Applicant](#) in all matters related to the procedure. The Agency scientific advice officer will have a background as a medical doctor, pharmacist or other scientific university degree.

They should be informed about any direct interaction between the applicant and the Coordinators. Applicants are therefore requested to copy all relevant correspondence as well as additional documentation requested by Coordinators to the appointed scientific officer at the Agency Secretariat.

The Agency secretariat additionally provides scientific, technical, and administrative support to the SAWP with a view to the performance of its duties and provides secretarial services. Below are some of the most important tasks listed:

- Act as a single point of contact for the Applicant requesting scientific advice, supporting the execution of the procedure in an efficient and high-quality manner.
- Carry out the validation of the advice procedures.
- Manage the [scientific aspects of the](#) procedure.
- Undertake [early informal dialogue in preparation of an application and preparatory and briefing meetings \(the latter are very early meetings to discuss future submissions of a request for scientific advice /protocol assistance\)](#) with [the](#) Applicants.
- Ensure that all relevant information is shared [and agreed](#) between COMP, CHMP, CAT, HMPC ~~and~~, PDCO ~~and~~ PRAC or other working parties as needed.
- Ensure that all relevant information from scientific advice and protocol assistance is included in the [IRISIRIS](#) platform, which shall contribute to the scientific support brought about by EMA both in terms of regulatory and scientific memory.
- Organise legal and regulatory support to the SAWP.
- Prepare the work of the SAWP in consultation with the chairperson [and the assigned Coordinators](#).
- Propose additional expertise including patients' representatives if necessary for orphan and non-orphan conditions.
- Ensure consistency between advice given, guidelines and CHMP assessment within the same therapeutic area, and contribute to the peer review by SAWP, CHMP and EMA of scientific advice/protocol assistance.
- Prepare the final letter for adoption by the SAWP/CHMP and COMP (when applicable).
- Ensure adequate co-ordination of the work carried out within the SAWP.

~~For further details, please refer to the [Mandate, Objectives and Rules of Procedure of the scientific advice working party](#).~~

## ~~18-17.~~ **When and how should I ask for a preparatory meeting for scientific advice ~~or for~~ /protocol assistance?**

A preparatory teleconference for scientific advice or for protocol assistance can be requested at time of submission of the application.

The Agency emphasises the importance of scientific advice or protocol assistance preparatory meetings with Applicants, especially for first users of these procedures, ~~for SMEs, for broad advice, and complex products or procedures e.g. WHO collaboration submission, FDA Parallel Advice, academic groups or micro, small and medium sized enterprises (SMEs) and innovative products or complex (regulatory or scientific) procedures, WHO collaboration submission, FDA Parallel Advice, or requests of Qualification of novel methodology.~~ Preparatory meetings are an opportunity for Applicants to:

- Introduce and receive feedback on their proposed development programme from the responsible Agency staff.
- Confirm the relevance of the request, and acceptability of the questions included therein, in line with the scope of EMA SA/PA
- Receive feedback on the questions ~~to be included in the request for scientific advice, and related Applicant's positions,~~ with a view ~~of~~ obtaining satisfactory answers (i.e., content and scope of questions; and structure of the request).
- Identify additional issues to be included in the request for scientific advice/protocol assistance.
- Obtain more detailed information concerning the procedure for obtaining scientific advice/protocol assistance.
- Ask regulatory questions to EMA, which are outside the scope of scientific advice. (please also refer to Question 3).
- Establish ~~personal~~ contact with the Agency staff closely involved with the application as it proceeds.

The preparatory meeting will also allow identification of additional expertise to be involved at an earlier stage in the procedure.

The Agency will try to accommodate requests on specific dates for the preparatory teleconference or face to face meeting. However, please be aware that it may not always be possible to arrange a meeting on the exact date requested. Agency scientific advice officers, ~~Product Team Leaders/Members, and secretariat staff~~ scientific officers from ~~the other~~ relevant ~~other committees/working parties~~ EMA functions, SME office or Regulatory Affairs representatives may participate in these meetings. No additional fee is levied for this option. The opinions expressed during a preparatory meeting will not prejudice the outcome of the advice procedures.

## ~~19.~~ **How will my request be validated?**

~~The request for scientific advice or protocol assistance is validated by the appointed scientific advice officer within the Agency Secretariat with regard to:~~

- ~~receipt of the Electronic Final package (final request) within the required deadline~~
- ~~structure and content of request including the scope of the questions~~

~~If one of these criteria is not according to requirements set out in this guidance, the request will not be considered valid and shall be postponed.~~

## ~~20.~~ **18. What is the scientific advice ~~or~~ /protocol assistance procedural timetable?**

The procedure is divided into 2 phases:

- a planning phase with/without a preparatory meeting, and
- an evaluation phase without discussion meeting (40 day) OR with a discussion meeting (70 day)

### **1a) Planning phase with Preparatory meeting**

<b>DAYS (calendar days)</b>	<b>ACTION</b>
~ D -45	<ul style="list-style-type: none"> <li>• The Applicant <b>submits an application including a draft briefing <del>document</del>package</b> for SA or PA requests to the EMA Secretariat via <u>IRIS-IRIS</u>.</li> </ul>

	<ul style="list-style-type: none"> <li>The application is forwarded by the Agency Secretariat to the SAWP for <b>appointment of two Coordinators</b> and, where appropriate, a Coordinator for questions relating to significant benefit (only applicable for PA).</li> </ul>
~ D -45 to Date of Preparatory meeting	<b>Organisation of Preparatory meeting</b> <ul style="list-style-type: none"> <li>Submission of the SA or PA request.</li> <li>Agency appoints in-house personnel, with following actions: <ul style="list-style-type: none"> <li>Agency review of evidence: scientific memory (previous and ongoing MAA), including checking existing EPARs and previous advice, literature review.</li> </ul> </li> <li>Additional Experts/patient representative identification.</li> </ul>
Date of Preparatory meeting	<b>Preparatory meeting</b> <ul style="list-style-type: none"> <li>Preparatory meeting with Agency secretariat.</li> <li>List of Comments (LoC) is forwarded to the Applicant. This document will be prepared by the Agency in order to improve validation of SA/PA requests, and flag issues identified at the preparatory meeting to the SAWP.</li> <li>Identify requests for which expertise is particularly needed.</li> <li>Working Party consultation (ad-hoc).</li> </ul>
~ D -5	<b>Validation of <del>revised draft</del>updated briefing package</b> <ul style="list-style-type: none"> <li>The Applicant <b>revises the briefing document</b> and <del>includes potential additional issues</del>as advised.</li> <li>Submission of revised draft briefing document, <b>both clean and with track changes</b>, to the Agency Secretariat</li> <li>Further comments might be sent from the scientific officer to the Applicant.</li> </ul>
~ D -3	<b>Validation of electronic final package</b> <ul style="list-style-type: none"> <li>Positive validation of <del>draft at</del>updated briefing package by the Agency Secretariat <b>and submission of final clean version, if necessary</b>.</li> </ul>

## 1b) Planning phase without Preparatory meeting

DAYS	ACTION
~ D -20	<ul style="list-style-type: none"> <li>The Applicant <b>submits an application including a draft briefing document</b> for SA or PA requests to the EMA Secretariat via <del>IRIS</del>-IRIS.</li> <li>The application is forwarded by the Agency Secretariat to the SAWP for <b>appointment of two Coordinators</b> and, where appropriate, a Coordinator for questions relating to significant benefit (only applicable for PA).</li> </ul>
~ D -15	<b>Validation of draft</b> <ul style="list-style-type: none"> <li>Agency review of evidence: scientific memory (previous and ongoing MAA), including checking existing EPARs and previous advice, literature review.</li> <li>Additional Experts/patient representative identification.</li> <li>If applicable, comments on the briefing document/package are forwarded to Applicant in writing.</li> </ul>
~ D -5	<b>Validation of <del>revised draft</del>updated briefing package</b> <ul style="list-style-type: none"> <li>The Applicant revises the briefing document <del>and includes potential additional issues</del>as advised.</li> <li>Submission of revised draft package, <b>both clean and with track changes</b>, to the Agency Secretariat</li> <li>Further comments might be sent from the scientific officer to the Applicant.</li> </ul>
~ D -3	<b>Validation of electronic final package</b> <ul style="list-style-type: none"> <li>Positive validation of <del>draft at</del>updated briefing package by the Agency Secretariat <b>and submission of final clean version, if necessary</b>.</li> </ul>

## 2) Evaluation phase

~ D +20	<ul style="list-style-type: none"> <li>The <b>Coordinators</b> send their <b>first reports</b> to the Agency Secretariat.</li> <li>The reports are forwarded for comments to the SAWP, the relevant Working Parties, <del>and Committees, and</del> the additional experts, <del>PDCO experts, and to the COMP (for PA), and/or patient representatives involved.</del></li> <li>Agency quality-assurance: <del>scientific memory (previous MAA), regulatory context,</del> literature review, checking existing EPARs and previous advice (<del>scientific memory</del>).</li> <li><del>The Applicant may be asked to provide further information or clarifications in preparation of the first reports discussion.</del></li> </ul>
~ D +30	<b>SAWP 2</b> <ul style="list-style-type: none"> <li>Discussion of the first reports focusing on <b>controversial issues</b>.</li> <li>The SAWP confirms at this stage whether the advice can be adopted at Day 40 or whether it is necessary to invite the Applicant for a discussion meeting (Day 70 procedure <del>e.g. in case of disagreement with the proposed development</del>), <del>refer to the following question</del>). In the latter case, a <b>list of issues</b> to be addressed by the Applicant at the discussion meeting is adopted by the SAWP and forwarded to the Applicant. The Applicant may also propose <del>in writing</del> to the Agency additional points for discussion that are not part of the adopted list of issues <del>and submit. These are to be submitted</del> in writing ahead of the Discussion meeting. Amendments/changes to the development programme should be notified to the Agency /SAWP ahead of the discussion meeting.</li> <li>The SAWP may <del>rarely</del> request the Applicant to address issues in writing only. In this case a list of issues to be addressed in writing is adopted by the SAWP and sent to the Applicant. <del>In this case and</del> the 70-day procedure will apply.</li> </ul>

### 2a)- no discussion meeting - 40-day procedure

The SAWP decides that there is no need for a discussion meeting and that the procedure can be finalised in 40 days.

~ D +33	<ul style="list-style-type: none"> <li>The <b>Coordinators</b> send their <b>joint report</b> to the Agency Secretariat.</li> </ul>
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	<ul style="list-style-type: none"> <li>The joint <b>Coordinators'</b> report and the draft advice letter to the Applicant are adopted by the SAWP through a <i>written procedure</i>.</li> <li>CHMP/SAWP/Agency peer review (content/consistency/coherence).</li> </ul>
~ D +40	<b>CHMP 2</b> <ul style="list-style-type: none"> <li>The <b>final advice letter is adopted</b> by the CHMP (and by the COMP in case of question on significant benefit for PA) and sent to the Applicant.</li> </ul>

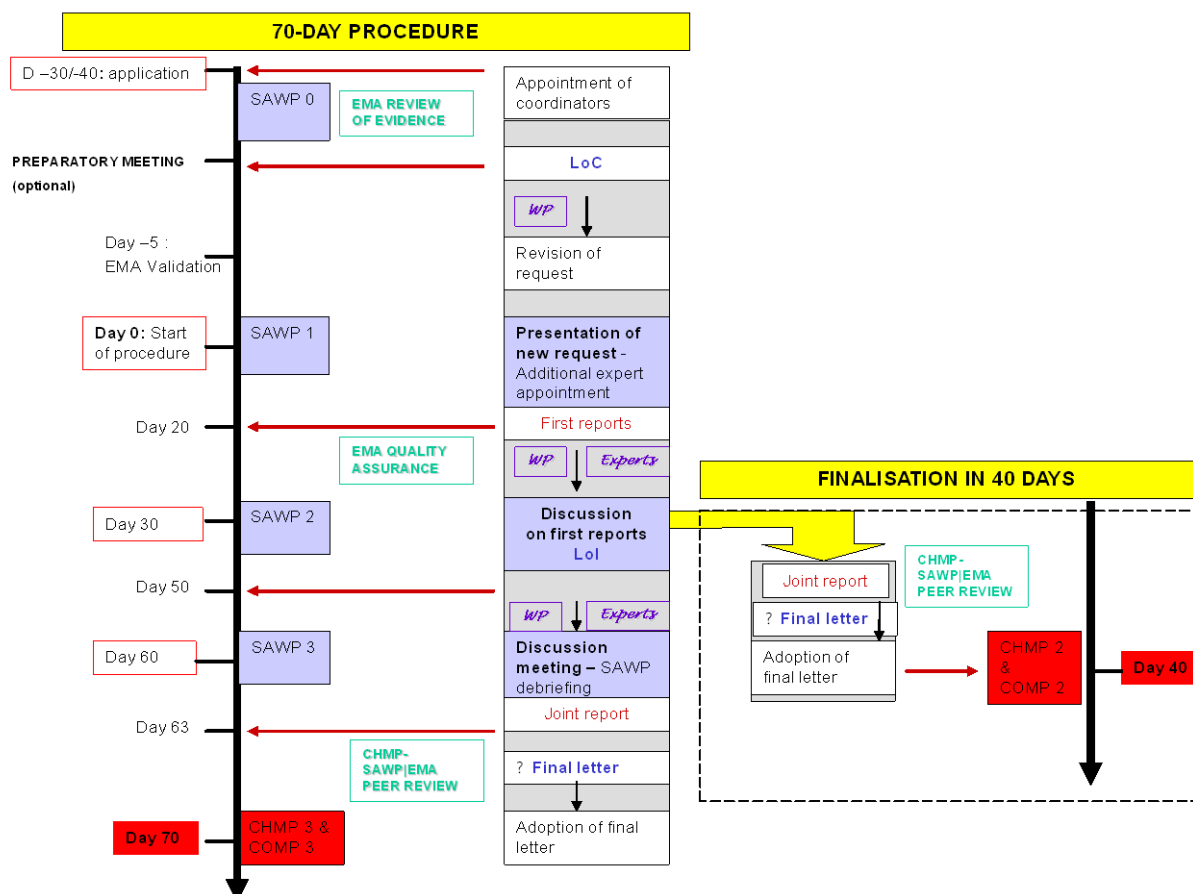
## 2b) with discussion meeting - 70-day procedure

The SAWP decides that there is a need for a discussion meeting and that the procedure be finalised in 70 days.

~ D +60	<b>SAWP 3</b> <ul style="list-style-type: none"> <li><b>Discussion meeting with Applicant and SAWP.</b></li> <li><b>The Coordinators present a preliminary conclusion at the end of the discussion meeting.</b></li> <li><b>The Coordinators present the outcome of the discussion meeting to the SAWP.</b></li> </ul>
~ D +63	<ul style="list-style-type: none"> <li>The <b>Coordinators</b> send their <b>joint report</b> to the Agency Secretariat.</li> <li>The joint <b>Coordinators'</b> report and the draft advice letter to the Applicant are adopted by the SAWP through a <i>written procedure</i>.</li> <li>CHMP/SAWP/ Agency peer review (content consistency/coherence).</li> </ul>
~ D +70	<b>CHMP 3</b> <ul style="list-style-type: none"> <li>The <b>final advice letter is adopted</b> by the CHMP (and by the COMP in case of question on significant benefit for PA) and sent to the Applicant</li> </ul>

Please note that throughout the procedure the Agency Secretariat gives detailed instructions and information on applicable timelines both to the Applicant and to the Coordinators.

### Overview of Procedure





## ~~21-19.~~ **How do I prepare for a Discussion meeting?**

At D+30 of the procedure (see also "timetable" for obtaining scientific advice or protocol assistance) the SAWP will discuss the Coordinators' first reports. It will be decided at this stage, whether to invite the Applicant for a discussion meeting.

The decision to invite the Applicant will be made by the SAWP on a case-by-case basis following the identification of the issues, ~~which need~~ to be discussed ~~by~~with the Applicant. ~~In case of SAWP An invitation for discussion meeting can be triggered by, e.g., a~~ disagreement with the Applicant's development ~~plans; plan proposed, divergent views among the Applicant will may be invited to a discussion meeting. For Advanced therapy products reviewers, the applicant will be invited to a need to clarify or receive more information on the development strategy and discuss alternative options.~~ Discussion ~~meeting~~meetings are part of the procedure by default in ~~the majority of cases. case of~~ Qualification Advice/Opinion requests or to allow multi-stakeholders interaction in case of parallel EMA-FDA scientific advice (PSA) or Joint Scientific Consultation with EUnetHTA.

The ~~scientific officer~~Agency will inform Applicants of the decision (40-day vs. 70-day procedure) at the end of the SAWP meeting at which the first reports are discussed. Applicants will be given an indication of the likely dates for the discussion meeting (usually day 2 and 3 of the following SAWP meeting). Applicants should ensure at the beginning of the scientific advice procedure, that, in case they are invited to a Discussion meeting, their relevant experts are available on/around D+60 in order to participate in such meetings.

When the need for a Discussion meeting is agreed by the SAWP, the Coordinators and other SAWP members may nominate additional experts to participate in the meeting including patients' representatives. In addition, the meeting will be open to all SAWP members.

A detailed list of issues to be addressed by the Applicant during the Discussion meeting will be adopted (D+30) and sent to the Applicant following the SAWP meeting.

The list of issues is divided in two categories:

- Issues to be addressed during the Discussion meeting
- Issues to be addressed in writing by the Applicant prior to the Discussion meeting

The Applicant may also propose additional points for discussion at the meeting. These must relate to the topics initially raised in the request submitted. Additional points should be forwarded in writing to the Agency secretariat for the attention of the scientific officer, at least a week before the meeting.

Furthermore, if upon receipt of the list of issues, the Applicant intends to present at the discussion meeting major amendments to the development initially proposed, a document summarising the main changes of the quality/non-clinical/clinical development programme should be provided to the Agency two weeks in advance of the meeting.

The Discussion meeting will take place at the Agency at D+60 during the SAWP meetings (see Dates of forthcoming SAWP meetings).

The Applicant will be informed of the exact timing of the discussion meeting approximately 10 working days before the SAWP meeting in question. Please contact the EMA scientific officer if you wish to know more about the preparation for the Discussion Meeting.

The Applicant's list of participants should be forwarded to the Agency 3 working days prior to the meeting, with the draft presentation submitted at least 3 working days before the start of the SAWP meeting in question.

On the day of the Discussion meeting, the Applicant will be asked to bring both an electronic copy (memory stick) ~~and hard copies (hand-outs)~~ of the MS PowerPoint presentation. ~~Hand-outs are circulated during the meeting.~~

Since March 2020 and due to the COVID-19 pandemic, the EMA is holding discussion meetings in virtual format only. This obviously allows for much more logistical flexibility in terms of Applicant attendees and minor last-minute changes to the presentation besides obviating the need for travelling to the Agency.

In most cases, 90 minutes will be allocated to each discussion meeting including: SAWP participants' internal briefing meeting, presentation and discussion on the topics. It is advised that each issue in the "List of Issues" document is addressed separately and that the discussion between the Applicant and the SAWP participants follows the presentation of each separate ~~topic's presentation~~.

All participants will be introduced by the Chairperson (one of the two Coordinators). The presentation should focus exclusively on the list of issues sent by the Agency (after a couple of introductory slides-), unless agreed otherwise. Preliminary conclusions will be drawn at the end of the discussion meetings, pending formal adoption of advice in the plenary SAWP/CHMP meetings.

Following the meeting with the Applicant, there will be a debriefing by the coordinators at the SAWP plenary meeting, in order to further discuss issues and to draw conclusions.

The Applicant will receive the names of all participants of the meeting on the next day.

The Applicant will be asked to provide minutes of the meeting 2 working days after the Discussion meeting. The minutes will be received by SAWP members, and the experts present *for information*. Minutes are regarded as an Applicant's record of the meeting and will not be endorsed by the SAWP.

## ~~22. What is the role of the scientific advice Working Party (SAWP)?~~

~~The SAWP is a permanent working party of the CHMP charged with drafting scientific advice, and protocol assistance for orphan medicinal products.~~

~~The SAWP is a multidisciplinary expert group and includes the chairperson and up to 36 members, among which 1 vice chairperson and at least 1 and not more than 3 members from each of the other EMA scientific committees.~~

~~The SAWP co-ordinates the provision of scientific advice and protocol assistance and brings forward to the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Orphan Medicinal Products (COMP) an integrated view as regards quality, non-clinical, clinical safety and efficacy, relating to the development of medicinal products and orphan medicinal products, and as regards significant benefit relating to orphan medicinal products.~~

~~In addition to its own expertise, the SAWP involves appropriate expertise (internal or external experts, Committees, Working Parties or Ad Hoc groups) whenever necessary, in particular in the provision of protocol assistance for orphan medicinal products intended for rare diseases, products for the development in children (Paediatric Committee-PDCO) and for the development of Advanced therapies (CAT).~~

~~The SAWP meets 11 times per year at the Agency for a 4 day meeting generally set 2 weeks before the CHMP (Dates of forthcoming meetings are published on the EMA website). The meeting is generally organised as follows: the first day is allocated for the SAWP plenary meeting on discussion of 1<sup>st</sup>~~

~~reports and the following days include both plenary discussions and Discussion meetings which are run up to five in parallel.~~

## ~~23-20.~~ **Is scientific advice ~~or~~ / protocol assistance binding?**

Applicants seeking scientific advice under Article 57-1 (n) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, or protocol assistance under Article 6 of the Regulation on Orphan Medicinal Products (EC) 141/2000 must note that any scientific advice or protocol assistance given is not legally binding with regard to any future marketing authorisation application of the product concerned, either on the Agency/CHMP/COMP, or on the Applicant.

The answer given is based on the question and documentation submitted without prejudice to evolution and developments in the state-of-the-art.

Furthermore, Applicants should note that the advice provided is without prejudice to applicable legislation relating to the particulars and documents, which must be submitted in support of a marketing authorisation application. It is also without prejudice to any intellectual property rights of third parties.

When providing scientific advice or protocol assistance, the CHMP or COMP (for questions related to demonstration of significant benefit within the scope of protocol assistance) do not pre-empt the outcome of the evaluation of any subsequent marketing authorisation application.

Advice will be given in good faith, but circumstances could change, especially in the case of early advice or subsequent scientific developments. In some cases, e.g. ~~as~~ as a result of scientific developments, an alternative approach to that advised may be ~~appropriate~~ preferred. In this case it is recommended to Applicants to request [a follow-up](#) to the initial scientific advice or protocol assistance given.

However, where Applicants choose not to apply the advice, they are requested to ~~clearly~~ justify ~~clearly~~ their position in any subsequent marketing authorisation application.

## ~~24-21.~~ **Is ~~a~~ clarification of the scientific advice ~~or~~ / protocol assistance possible?**

If needed, the Applicant may request a clarification after receipt of the final advice letter. This is *only* intended to provide the Applicant with the opportunity to ~~clarify~~ request clarification on the meaning of CHMP advice ~~that is if~~ perceived as ~~not~~ being ~~not~~ clear or precise enough. Any new information, new data, a new Applicant's position, or a request to amend the advice already given would normally require a follow-up advice procedure rather than a clarification, as time and resources have to be organised for its evaluation.

~~The Applicant should preferably first contact by phone or via IRIS the scientific officer in charge of the procedure.~~

The request for clarification shall ~~only~~ be sent to the Agency via IRIS. The request should clearly state what is perceived as being unclear in the scientific advice or protocol assistance letter. The request will be reviewed by the scientific officer in charge of the procedure. Minor clarification will be addressed with the Coordinators in writing in an expedited manner. Major clarifications will be addressed at the following SAWP meeting.

## ~~25-22.~~ **22. Is a follow-up of the scientific advice or/protocol assistance possible?**

Applicants may ask for a "follow-up" to the initial request for scientific advice or protocol assistance.

A ~~Follow~~follow-up to initial request is defined as any subsequent request falling within the same therapeutic indication and discipline as the initial request (discipline (area) means quality, safety and/or clinical development including pharmacovigilance/risk management aspects).

A follow-up to the initial request can typically be requested to reconsider the scientific advice or protocol assistance already given in the light of new information available to the Applicant or in case of changes or amendments to the development programme for which scientific advice or protocol assistance was given. When submitting a follow-up to the initial request for scientific advice or protocol assistance, the Applicant should refer to the previous CHMP advice and highlight supported with detailed justifications, the issues to be reconsidered.

~~The Applicant will be asked to forward new information and all supporting documents in accordance with the CHMP requirements regarding structure and content of the scientific advice or protocol assistance request.~~

The procedure for requesting a follow-up advice follows the same outline as a request for initial advice:

The Agency Secretariat should be formally notified of the intent to submit a follow-up scientific advice or protocol assistance request. The structure/content of the follow-up request should follow the format specified ~~as~~ for the initial scientific advice/protocol assistance.

The procedure (timetable) in place for provision of a follow-up scientific advice or protocol assistance is usually completed in 40 Days. If necessary, the Applicant will be invited to a Discussion Meeting, and a 70-day procedure will apply.

## ~~26-23.~~ **23. Will scientific advice or/protocol assistance be published?**

After each CHMP, an overview of the number of final scientific advice or protocol assistance letters adopted, with ~~broad detail~~high-level information on the substance(s) (biological, chemical or other), the intended indication(s), the type of request (new request or follow-up) and the topic (pharmaceutical, non-clinical, clinical or significant benefit) is published in the CHMP ~~Monthly report~~monthly highlights. The number of new requests accepted by the Committee is provided as well. For ~~example~~more information please ~~see~~refer to the list of monthly highlights under [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2013/03/WC500140683.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/03/WC500140683.pdf) CHMP: Agendas, minutes and highlights | European Medicines Agency (europa.eu).

However, the ~~actual~~scope, content and outcome of a scientific advice or protocol assistance ~~outcome~~ given by the CHMP ~~for a medicinal product is considered, other than a qualification opinion, remain~~ confidential and ~~will~~is not be made public prior to the submission of an application for a marketing authorisation or during the assessment of such marketing authorisation~~published~~. In addition, scientific advice or protocol assistance outcomes will not be shared with other Applicants.

In case of a subsequent centralised marketing authorisation, a high-level summary of the scientific advice or protocol assistance given by the CHMP ~~will be~~for that indication is included in the EPAR, after deletion of commercially confidential information.

The names of the scientific advice Coordinators ~~will be~~are also mentioned.

The [Scientific Advice Working Party](#) ~~will monitor~~monitors the scientific advice or protocol assistance requests to identify where new guidelines or ~~an~~ update of ~~earlier~~existing guidelines are needed. ~~This will be highlighted to and inform~~ the CHMP accordingly. The CHMP may decide on the need for the development of general or product specific guidance to industry ~~in form of notes for guidance etc. for certain scientific areas where scientific advice is frequently requested.~~ Standard. Questions & Answers documents for frequently asked questions may also be developed by the relevant working parties and published on the Agency website.

## **~~27-24.~~ Is it possible to approach the European Medicines Agency and US Food and Drug Administration (FDA) for parallel scientific advice?**

An exchange of views between the EMA and the FDA is possible and encouraged for global drug development programmes.

Parallel scientific advice should focus primarily on important breakthrough drugs or important safety issues in the following areas which have been identified as clusters of interest between the agencies: Oncology, Vaccines, Orphan Drugs, drugs in the Paediatric Population, Nanotechnologies, Advanced Therapies, Pharmacogenomics and Blood products. Parallel scientific advice procedures are conducted under the auspices of the confidentiality arrangement between the European Commission, the EMA, and FDA.

If the request is submitted in a synchronised manner to the FDA and the EMA, similar procedural timelines allow for discussion before the final decision is reached by each agency.

This exercise is not intended to provide a combined or joint advice from the two regulatory authorities but is an opportunity for increased dialogue and possible convergence in terms of development requirements. Each agency will provide their independent advice to the Applicant.

These requests should preferably coincide with an End-of-Phase 2 or pre-IND meeting at the FDA. Depending on the nature of the issues, the discussion between the agencies might take the form of an exchange of documents, a teleconference or a videoconference. A Discussion meeting with the Applicant will always take place.

Applicants considering using this procedure should contact both agencies as early as possible, taking into account the general principles as published in the document: [General Principles EMA FDA Parallel scientific advice](#).

## **~~28-25.~~ Is it possible to approach the European Medicines Agency and Health Technology Assessment (HTA) bodies for parallel scientific advice?**

Applications for CHMP scientific advice/protocol assistance and advice from Health Technology Assessment bodies in parallel are possible and welcome. Please contact the EMA scientific advice secretariat directly through the general scientific advice inbox: [scientificadvice@ema.europa.eu](mailto:scientificadvice@ema.europa.eu) to arrange a discussion on this process if you are considering putting in such a request. Please see the current [Guidance on Parallel Joint Scientific Consultation](#) incorporating EMA and the European Network of HTAs (EUnetHTA) EMA/798877/2022.

This platform and guidance replace the previous Best Practice Guidance for EMA-HTA parallel scientific advice and the associated procedure. For advice relating to HTA aspects and involvement in parallel consultations, Applicants are also advised to consult the EUnetHTA Joint Scientific Consultation at [EUnetHTA21-JSC@g-ba.de](mailto:EUnetHTA21-JSC@g-ba.de).

## **29-26. Is it possible to involve World Health Organisation (WHO) experts in scientific advice?**

Involvement of WHO experts is possible and encouraged for global drug development programmes, in particular for products submitted under Article 58 (EU-M4all).

The scientific advice procedures are conducted under the auspices of the confidentiality arrangement between the European Commission, the EMA, and WHO.

When applying for Scientific Advice the need for WHO involvement can be stated in the relevant field of the application form. If the applicant has already approached the WHO and been in contact with specific experts these should be communicated in the same application form as a note to facilitate logistics arrangements between the EMA and the WHO.