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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 Applicants to submit requests which are in conformity with Scientific Advice Working Party (SAWP) requirements and which can be validated and evaluated quickly and efficiently.

Furthermore, Applicants will be 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 include:

- Replacement of EMA/HTA parallel scientific advice by a new platform 'Parallel Consultation' incorporating EMA and EUnetHTA



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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 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 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 industry 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 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 Working Parties, drafting groups, the CHMP and the Agency Secretariat with input from other Committees where relevant such as CAT, PDCO, HMPC.

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 sponsor. Nevertheless, the advice provided is taken into consideration during 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 consultation does not preclude the possibility of consultations with 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 and safety of the product for pre- or post-authorisation activities including risk-management programmes). Scientific advice may be given on issues relating to interpretation and implementation of (draft) EU guidelines.

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 pre-evaluation of data to support a Marketing Authorisation application.

For advice or procedural guidance relating to biomarkers and qualification of novel methodologies for drug development, Applicants are also advised to consult [the Alternative 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 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 indications. For a broad advice the Agency strongly recommends to have scientific advice presubmission meetings.

- 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 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; EMEA/357981/2005).
- 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 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 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 paediatric developments.
- Scientific 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".
- The use of modelling and simulation for specific aspects of drug development.
- 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, 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 as defined in Article 83 of Regulation (EC) No 726/2004.
- Agency advice prior to submission for qualification of a request for an accelerated assessment procedure. Guideline on the procedure for [Accelerated assessment](#) pursuant to Article 14(9) of Regulation (EC) No726/2004 (EMA/419127/05).
- Paediatric Investigation Plans as defined in the Regulation (EC) No 1901/2006 on medicinal products for paediatric use, as amended. Advice on waivers, deferrals or specific regulatory issues that are the exclusive mandate of the Paediatric Committee.
- Regulatory aspects which are handled by the Agency Secretariat (e.g. discussion regarding legal basis for submission, format of marketing authorisation application and Common Technical Document etc.). Regulatory and administrative questions can be answered by the Agency Secretariat directly during a [scientific advice presubmission meeting](#) if pre-notified, or in writing, or at later meetings with the Agency.

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, paediatric geriatric development, 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 preclinical/clinical trials by literature, bridging strategy, safety database, risk management plans).

4. Protocol assistance particular issues

Specifically for protocol assistance, the questions and proposed development plan should 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) relating to the proposed future development of the orphan medicinal product within the scope of the designated indication.

Also 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 presubmission meeting](#) if pre-notified, or in writing, or at later meetings with the Agency.

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 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 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.

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.

Scientific advice or protocol assistance requested during the *post authorisation phase* are generally related but not exclusively restricted to the following cases:

- A new formulation or dosage form
- An extension of indication
- A new or a change of manufacturing process
- Post authorisation studies
- Post 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. This advice will be free of charge for paediatric-related questions. Applicants may choose to request scientific advice first, to help in the preparation of a paediatric investigation plan, or to submit a paediatric investigation plan directly and follow it up with a request for scientific advice on, for example, combined adult and paediatric development in light of the paediatric investigation plan requirements or discussions.

The procedure for requesting scientific advice/protocol assistance should be followed as indicated. It is important that the Applicant completes the relevant paediatric elements in the letter of intent, when submitted to the Agency.

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.

Where an Applicant has previously submitted a Paediatric investigation plan, and subsequently requests scientific advice/protocol assistance on the related paediatric development, it is recommended to include a comparative table in the briefing document for SAWP/CHMP outlining the differences or changes to the paediatric development programme compared to the previous submission to the Agency, where relevant.

Members of the Paediatric Committee will be invited by SAWP/CHMP to participate as individual experts during the scientific advice/protocol assistance procedure, where necessary. The EMA secretariat ensures relevant information is exchanged 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 notification of the administrative validation to the Applicant and fees will be payable within 45 calendar days of the date of the notification. For details please refer to the Explanatory note on fees payable to the European Medicines Agency.

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

Disciplines

- Quality development: chemical, pharmaceutical and biological testing.
- Safety development (nonclinical): toxicological and pharmacological tests.
- Clinical development: studies in human subjects in whether patients or non-patient volunteers, including clinical pharmacological trials designed to determine the efficacy and safety of the product.
- 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 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 clinical development, or
- quality and clinical development, or
- safety and clinical development
- qualification advice

Fee level II

For initial requests on:

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

Fee level I

For initial requests on:

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

Fee level II

For follow-up on:

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

Fee level I

For follow-up on:

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

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

It is no longer necessary to submit a separate fee reduction request for medicinal products with an Orphan designation. The fee reduction entitlement will be checked internally. Applicants should ensure that all necessary information relating to the orphan designation is included in the Letter of Intent for the procedure.

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. 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. Applicants should ensure that all necessary information relating to the SME status is included in the Letter of Intent for the procedure.

Where an SME Applicant could, in respect of the same fee, also benefit from other reductions provided for in Community legislation (e.g. 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 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

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

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 sent in to the Agency. The fee reduction will automatically be applied during the 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?

The Applicant submits a **Letter of Intent and draft package** for feedback (terms which may be used interchangeably include draft package, request or dossier.) See question 12.

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

The Applicant circulates the **Final validated Package**. See questions 13 and 14.

See below for further details. The same process applies for requests for follow up advice.

12. What is the letter of intent and draft package 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 a **Letter of Intent**.

A letter of intent should be sent by email to scientificadvice@ema.europa.eu, in advance of the anticipated start of the procedure. The latest PDF form provided on the [EMA scientific advice website](#) should be used.

The draft package 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 presubmission face to face meeting is requested with the letter of intent and draft package, the deadline is approximately 7 weeks before the intended start of the procedure. If no face to face presubmission meeting is requested the deadline for submitting the letter of intent and draft package is approximately 3 weeks before the intended start of the procedure.

The [dates of forthcoming SAWP meetings](#) and deadlines for scientific advice or protocol assistance letters of intent and request 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 presubmission meeting, the applicant revises the draft package as needed and resubmits the electronic final package (referred to as final request in the published submission deadlines) which will be [validated](#) by the scientific advice officer.

Circulating the validated package (request/dossier)

Once validated, the final package should be forwarded as **an electronic copy** via Eudralink to the Agency and to the 2 appointed Coordinators as instructed during the validation process.

The briefing document including the question(s)/Applicant's position(s) should be submitted 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 delivery 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 dossier could result in a delay of the procedure by one month.

15. What is the role of the SAWP Coordinator?

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 Working Parties and the CHMP and their experts.

Should a face to face [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 Coordinator(s).

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. All experts are bound by a confidentiality agreement.

16. What is the procedure for appointment of Coordinators?

Subsequently to the submission of the Letter of Intent, 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 SAWP meeting at D-30. The timing for nomination is the same irrespective of presubmission meeting or not.

For centralised applications, the appointment of Rapporteurs/Co-Rapporteurs 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 Rapporteurs/Co-Rapporteurs for centralised applications.

Following the appointment of Coordinators at the SAWP meeting, the applicant will receive an e-mail indicating the names of the appointed Coordinators and the responsible Agency scientific officer.

17. What is the role of the Agency scientific officer/ Agency Secretariat?

The Agency **scientific officer** is the contact person for the 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 procedure.
- Undertake presubmission and briefing meetings (the latter are very early meetings to discuss future submissions of a request for scientific advice /protocol assistance) with Applicants.
- Ensure that all relevant information is shared between COMP, CHMP, CAT, HMPC and PDCO or other working parties as needed.
- Ensure that all relevant information from scientific advice and protocol assistance is included in the scientific advice database, 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.
- 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. When and how should I ask for a presubmission meeting for scientific advice or for protocol assistance?

A presubmission teleconference or face to face meeting for scientific advice or for protocol assistance can be requested at time of submission of the [letter of intent](#). Following a pre-review of the briefing package, the Agency Officer may also advise the Applicant on the need for a (teleconference or face to face) meeting or not.

The Agency emphasises the importance of scientific advice or protocol assistance presubmission 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.

Presubmission meetings are an opportunity for Applicants to:

- Introduce and receive feedback on their proposed development programme from the responsible Agency staff.
- Receive feedback on the questions to be included in the request for scientific advice 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, which are outside the scope of scientific advice.
- Establish personal contact with the Agency staff closely involved with the application as it proceeds.

The presubmission 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 presubmission 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 from the relevant other committees/working parties, SME office or Regulatory Affairs may participate in these meetings. No additional fee is levied for this option. The opinions expressed during a presubmission 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:

- a) receipt of the Electronic Final package (Final request) within the required deadline
- b) 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. What is the scientific advice or protocol assistance procedural timetable?

The procedure is divided into 2 phases:

- a planning phase with/without a [presubmission meeting](#), and
- an evaluation phase without discussion meeting (40 day) OR with a discussion meeting (70 day)

1a) Planning phase with Presubmission meeting

DAYS (calendar days)	ACTION
~ D -45	<ul style="list-style-type: none"> • The Applicant submits a letter of intent and draft briefing package for SA or PA requests to the EMA Secretariat. • The letter of intent and draft briefing package are forwarded by the Agency Secretariat to the SAWP for appointment of 2 Coordinators and, where appropriate, a Coordinator for questions relating to significant benefit (only applicable for PA).
~ D -45 to Date of Presubmission meeting	<p>Organisation of Presubmission meeting</p> <ul style="list-style-type: none"> • Submission of the SA or PA request. • Agency appoints in-house personnel, with following actions: <ul style="list-style-type: none"> ○ Agency review of evidence: scientific memory (previous and ongoing MAA), including checking existing EPARs and previous advice, literature review. • Additional Experts/patient representative identification.
Date of Presubmission meeting	<p>Presubmission meeting</p> <ul style="list-style-type: none"> • Presubmission meeting with Agency secretariat. • 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 presubmission meeting to the SAWP. • Identify requests for which expertise is particularly needed. • Working Party consultation (ad-hoc).
~ D -5	<p>Validation of revised draft</p> <ul style="list-style-type: none"> • The Applicant revises the briefing document and includes potential additional issues. • Submission of revised draft package to the Agency Secretariat • Further comments might be sent from the scientific officer to the Applicant.
~ D -3	<p>Validation of electronic final package</p> <ul style="list-style-type: none"> • Positive validation of draft at the Agency Secretariat
~ D -3	<p>Submission</p> <ul style="list-style-type: none"> • Submission of final dossier via Eudralink from Applicant to the Agency Secretariat and to the nominated Coordinators. • The validated SA or PA request is forwarded by the Agency Secretariat to the SAWP and to the relevant Working Parties.

1b) Planning phase without Presubmission meeting

DAYS	ACTION
~ D -20	<ul style="list-style-type: none"> • The Applicant submits a letter of intent and draft briefing package for SA or PA requests to the EMA Secretariat. • The letter of intent and draft briefing package are forwarded by the Agency Secretariat to the SAWP for appointment of 2 Coordinators and, where appropriate, a Coordinator for questions relating to significant benefit (only applicable for PA).
~ D -15	<p>Validation of draft</p> <ul style="list-style-type: none"> • Agency review of evidence: scientific memory (previous and ongoing MAA), including checking existing EPARs and previous advice, literature review. • Additional Experts/patient representative identification. • If applicable, comments on the briefing document/package are forwarded to Applicant in writing.
~ D -5	<p>Validation of revised draft</p> <ul style="list-style-type: none"> • The Applicant revises the briefing document and includes potential additional issues. • Submission of revised draft package to the Agency Secretariat

	<ul style="list-style-type: none"> Further comments might be sent from the scientific officer to the Applicant.
~ D -3	Validation of electronic final package <ul style="list-style-type: none"> Positive validation of draft at the Agency Secretariat
~ D -3	Submission <ul style="list-style-type: none"> Submission of final dossier via Eudralink from Applicant to the Agency Secretariat and to the nominated Coordinators. The validated SA or PA request is forwarded by the Agency Secretariat to the SAWP and to Working Parties.

2) Evaluation phase

~ D +20	<ul style="list-style-type: none"> The Coordinators send their first reports to the Agency Secretariat. The reports are forwarded for comments to the SAWP, the relevant Working Parties, the additional experts, PDCO experts, and to the COMP (for PA). Agency quality-assurance: scientific memory (previous MAA), literature review, checking existing EPARs and previous advice.
~ D +30	SAWP 2 <ul style="list-style-type: none"> Discussion of the first reports focusing on controversial issues. 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 e.g. in case of disagreement with the proposed development). In the latter case, a list of issues to be addressed by the Applicant at the discussion meeting is adopted by the SAWP and sent to the Applicant. The Applicant may also propose in writing to the Agency additional points for discussion that are not part of the adopted list of issues and submit 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. The SAWP may 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. In this case the 70-day procedure will apply.

2a) no discussion meeting - 40-day procedure

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

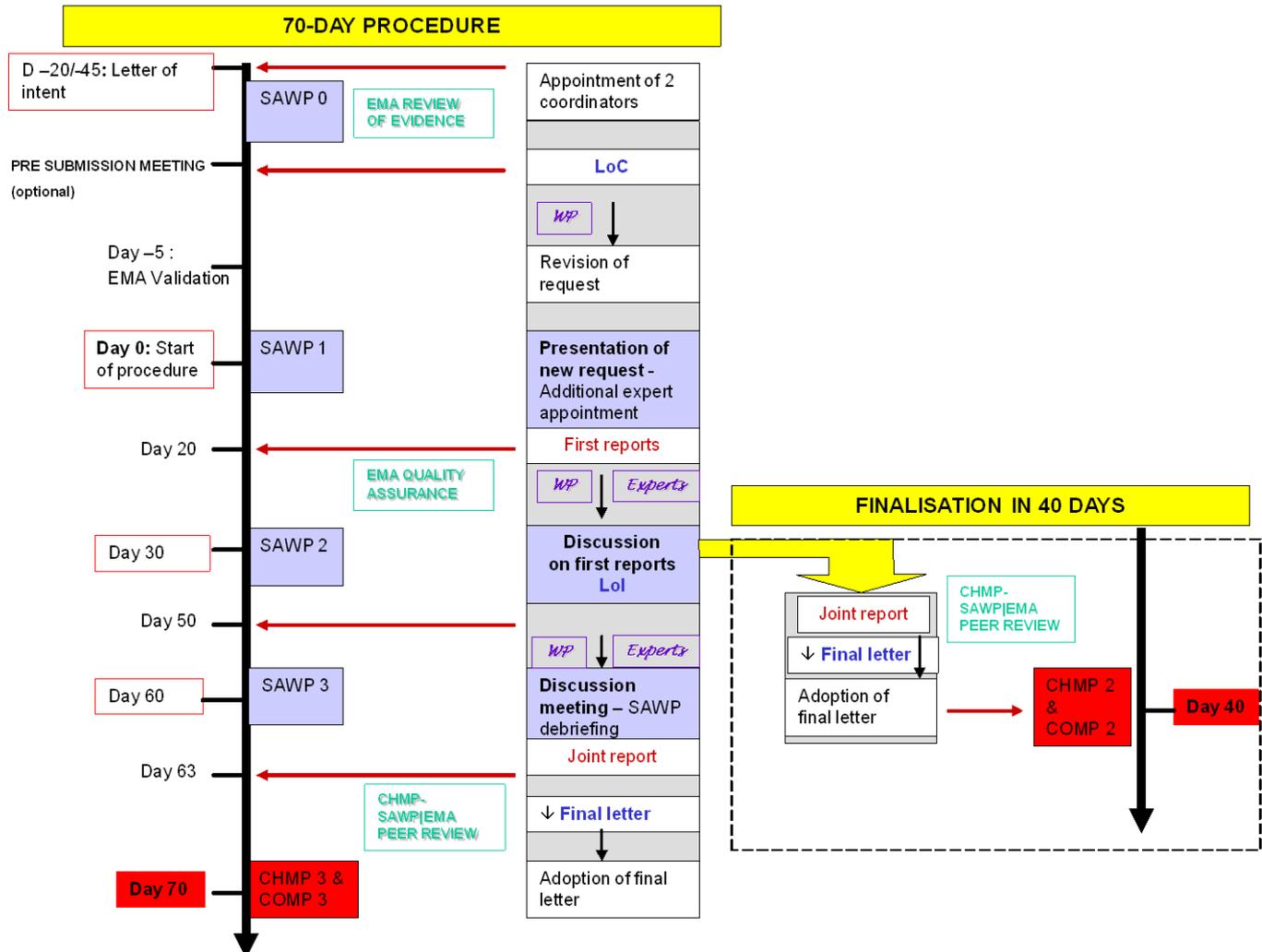
2b) with discussion meeting - 70-day procedure

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

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

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. 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 the Applicant. In case of SAWP disagreement with the Applicant's development plans, the Applicant will most likely be invited to a discussion meeting. For Advanced therapy products, the sponsor will be invited to a Discussion meeting in the majority of cases.

The scientific officer will inform Applicants by email of the decision (40 day vs. 70 day procedure) before 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, and preferences requested. In general, EMA will try to take these preferences into account, but this is not guaranteed and flexibility is required. 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 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.

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 preparation for the Discussion Meeting.

The Applicant's list of participants should be forwarded to the Agency 2 working days prior to the meeting, with the presentation submitted at least 2 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 electronic copy (memory stick) and hard copies (hand-outs) of the MS PowerPoint presentation. Hand-outs are circulated during the meeting.

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 each separate topic's presentation.

All participants will be introduced by the Chairperson (one of the two Coordinators) and nameplates will be provided. The presentation should focus exclusively on the list of issues sent by the Agency (after a couple of introductory slides). 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 by electronic mail.

The Applicant will be asked to provide minutes of the meeting 2 working days after the Discussion meeting. The minutes will be forwarded by the Agency Secretariat to the SAWP members and the experts present *for information*. Minutes are regarded as a 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 28 Members, among which 1 Vice-Chairperson, one member from the Committee for Advanced Therapies (CAT), one member from the Paediatric Committee and up to 3 Members from the Committee for Orphan Medicinal Products (COMP). The Chairperson of the SAWP is nominated by the CHMP for a term of three years, renewable. The Chair of SAWP may or may not belong to the CHMP. The Vice-Chairperson of the SAWP is elected by and from amongst SAWP members for a term of three years, renewable. The CHMP appoints 23 SAWP members for a term of three years, upon proposals from CHMP delegates. Three members are appointed by the COMP, one member from the PDCO and one member by the CAT.

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 3-4 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 1st reports and the following days include both plenary discussions and Discussion meetings which are run up to five in parallel.

23. 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 a result of scientific developments, an alternative approach to that advised may be appropriate. 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 justify clearly their position in any subsequent marketing authorisation application.

24. 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 the meaning of CHMP advice that is perceived as 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 resource have to be organised for its evaluation.

The Applicant should preferably first contact by phone or e-mail the scientific officer in charge of the procedure.

The request for clarification shall only be sent to the Agency by e-mail (in MS Word document) to the scientific officer in charge of the procedure. A document should clearly request 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 dossier. 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. 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-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 make reference to the previous CHMP advice and highlight 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. 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 details 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. The number of new requests accepted by the Committee is provided as well. For example, please see http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/03/WC500140683.pdf

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

In case of a subsequent centralised marketing authorisation, scientific advice or protocol assistance given by the CHMP will be included in the EPAR, after deletion of commercially confidential information.

The names of the Coordinators will be mentioned.

The [scientific advice Working Party](#) will monitor the scientific advice or protocol assistance requests to identify where new guidelines or an update of earlier guidelines are needed. This will be highlighted to the CHMP accordingly. The CHMP may decide on the need for the development of general 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. 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. 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](#) EMEA/24517/2009.

28. 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 to arrange a discussion on this process if you are considering putting in such a request. Please see the current Guidance on Parallel Consultation incorporating EMA and the European Network of HTAs (EUnetHTA) EMA/4260/2001 on [the EMA website](#).

This platform and guidance replaces 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 Early Dialogue secretariat at EUnetHTA-HAS@HAS-Sante.fr