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EMA procedural advice for medicinal products intended exclusively for markets outside the European Union under Article 58 of Regulation (EC) No 726/2004 in the context of co-operation with the World Health Organisation (WHO)

Introduction

This document addresses a number of questions that users of Article 58 of Regulation (EC) No 726/2004 may have. It provides an overview of the EMA's position on issues that are typically addressed in pre-submission meetings.

The EMA emphasises the importance of pre-submission meetings with applicants. These meetings are an opportunity for applicants to obtain procedural and regulatory advice to streamline the submission of their application. Together with the guidance in this document, successful pre-submission meetings should enable applicants to submit applications that conform to legal and regulatory requirements and that can be validated speedily. Pre-submission meetings also enable applicants to establish contact with the EMA product team who will be involved with the application as it proceeds.

In addition, applicants are actively encouraged to seek scientific advice as early as possible in the development process.

For further information on the contents of this document or other questions, please send an e-mail to article58@ema.europa.eu.

Instructions for users:

To obtain the information on a certain topic, click on the highlighted keyword. Although the information in this document should answer most queries, each application has its own particularities so we strongly encourage applicants to request a pre-submission meeting.

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1. What is the aim of the procedure laid down in Article 58 of Regulation (EC) No 726/2004?

Article 58 of Regulation (EC) No 726/2004 establishes a mechanism whereby the European Medicines Agency (EMA) may give a scientific opinion, in the context of cooperation with the World Health Organisation (WHO), for the evaluation of certain medicinal products for human use intended exclusively for markets outside the European Union.

Article 58 of the Regulation responds to the need to protect and promote public health and to give scientific assistance to non- EU countries in the context of cooperation with WHO whilst at the same time facilitating rapid access by those countries to important new medicinal products.

For this purpose, an application shall be submitted by the applicant to the Agency; the Committee for Medicinal Products for Human Use (CHMP) will, after consulting the World Health Organisation, draw up a scientific opinion. The CHMP scientific opinion assessment report includes elements on quality, safety and efficacy of the medicinal product and will conclude on the benefit-risk balance and conditions of use based on the intended populations and markets.

The application for this procedure does not exclude a future application for a marketing authorisation in the European Union.

References:

- Regulation (EC) No 726/2004 of the European Parliament and of the Council

2. Which medicinal products are eligible for evaluation under Article 58 of Regulation (EC) No 726/2004?

Medicinal products for human use are eligible for evaluation under Article 58 of Regulation (EC) No 726/2004 if they are intended **exclusively for markets outside the European Union**. Eligible products include medicines that are intended for the prevention or treatment of diseases of major public health interest. They include but are not limited to:

- vaccines that are or could be used in the WHO Expanded Program on Immunization (EPI);
- vaccines for protection against a WHO 'public health priority disease';
- vaccines that are part of a WHO-managed stockpile for emergency response;
- medicinal products for WHO target diseases such as human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), malaria, tuberculosis, lymphatic filariasis (elephantiasis), trachoma, leishmaniasis, schistosomiasis, African trypanosomiasis (sleeping sickness), onchocerciasis (river blindness), dengue fever, Chagas disease, leprosy and intestinal helminths.

Eligible products may include new formulations, new pharmaceutical forms or routes of administration of medicinal products already authorised in the European Union, fixed-dose combination products and generic products.

Applicants need to request eligibility for evaluation under Article 58 for a medicinal product before submitting an application. This request will be evaluated by the EMA's Committee for Medicinal Products for Human Use (CHMP), in collaboration with the WHO.

References:

- Regulation (EC) No 726/2004 of the European Parliament and of the Council

3. How are requests for eligibility submitted?

The eligibility request is made using the pre-submission request form, sent to the following address: article58@ema.europa.eu and CPEligibility@ema.europa.eu.

This request is free of charge and includes the following information:

- evidence that the applicant is based in the European Economic Area (EEA), or information of a contact point within the EEA;
- a justification for the product's eligibility for evaluation under Article 58 (see question 2). It is recommended that any available epidemiological data on the disease, data on disease burden and a summary of available efficacy or safety data also be submitted;
- a list of the countries in which the applicant intends to market the product;
- a statement that the applicant does not intend to market the medicinal product in the European Economic Area (EEA);
- a draft summary of product characteristics (SmPC) or a product profile including the proposed classification for the supply of the medicinal product;
- a justification or rationale for accelerated assessment, if appropriate.

Once eligibility has been confirmed, an applicant can request a pre-submission meeting in order to obtain guidance on the procedure.

4. How will data be exchanged between public authorities in the context of Article 58 activities?

The procedure laid down in Article 58 of Regulation (EC) No 726/2004 implies an exchange of information and data pertaining to eligibility, scientific advice or evaluation between the competent authorities (e.g. EMA and WHO).

The exchanges of confidential information between competent authorities are covered by confidentiality arrangements.

References

- WHO confidentiality arrangements

5. How is eligibility assessed?

The eligibility of a product for evaluation under Article 58 is assessed on a case-by-case basis by the EMA in consultation with the WHO.

Once the EMA has received a valid eligibility request from the applicant, it is sent for consultation to the WHO.

The EMA's Committee for Medicinal Products for Human Use (CHMP) will confirm eligibility taking into account the WHO's position. The outcome of the eligibility evaluation is sent to the applicant and, if eligibility is refused, the reasons are stated.

6. How long is eligibility valid for?

The validity of the eligibility of a medicinal product for evaluation under Article 58 will depend on the underlying information in support of the eligibility request. For cases where the epidemiological situation or environment has changed, the Applicant should request a reconfirmation of the eligibility by the EMA and WHO.

In cases where the eligibility was delivered more than 2 years prior to the application, the applicant may be requested to resubmit the eligibility request, and in particular if treatments have been authorised in the meantime or the epidemiological situation has substantially evolved. In order not to delay the nomination of Rapporteurs, and Experts and Observers from target countries nominated by the WHO and which is initiated 7 months before intended submission date, we would advise a re-confirmation request about 9 months prior intended submission date.

7. Does the applicant need to be established in the EEA?

Applicants or their contact points must be established in the EEA, i.e. in a Member State of the European Union (EU), Norway, Iceland or Liechtenstein. Evidence to support establishment in EEA must be provided both at the time of submitting an eligibility request and at the time of submission of the application.

8. Can applicants ask for scientific advice?

Yes, applicants are actively encouraged to ask for scientific advice on scientific questions concerning quality, non-clinical and clinical aspects. Such scientific advice is given by the CHMP's Scientific Advice Working Party (SAWP). Questions can also be related to adequacy of pharmacovigilance planning and/or risk minimisation measures to be implemented in the countries where the medicinal product is intended to be authorised.

Applicants can request scientific advice during the initial development of a product, before an application for CHMP scientific opinion or after an opinion has been granted.

In order to streamline regulatory activities based on Article 58 scientific opinions, in agreement with the applicant, experts from WHO or regulatory agencies in target countries may participate to the scientific advice procedure. The documentation provided as part of the scientific advice procedure will be circulated to the concerned experts unless specified otherwise by the applicant.

The timeframe for a standard scientific advice procedure is 40 days. This may be extended to 70 days if there is a need for a face-to-face meeting with the applicant.

Further information on the scientific advice procedure and a template for request for scientific advice are available on the EMA website 'Scientific Advice and Protocol Assistance'.

9. How much does scientific advice cost?

The standard fees for scientific advice will also apply for products to be evaluated under Article 58.

Scientific advice on paediatric questions is free of charge.

Small and medium-sized enterprises (SME) may be able to benefit from fee reductions for these scientific advices (see question 10).

Other applicants have also the possibility to request a total or partial waiver of the fee, which may be granted by the EMA's Executive Director on the recommendation of the CHMP. Requests for waivers should be sent to the Executive Director with appropriate justification as early as possible, but not later than three months prior to the anticipated date of submission of the application for scientific advice.

For more information on fees, please refer to Fees payable to the European Medicines Agency.

References:

- Fees payable to the European Medicines Agency
- EMA website 'Scientific Advice and Protocol Assistance'

10. Can an applicant apply for small and medium-sized enterprise (SME) status?

Applicants can apply for status as a small and medium-sized enterprise (SME). The EMA has set up an 'SME office', which offers assistance for SME status applications as well as financial and administrative assistance to registered SMEs. Details on how to register as an SME with the Agency are available on the EMA website 'Supporting SMEs'.

Fee incentives apply to SMEs established in the EU/EEA. If an enterprise is not yet legally established in the EU/EEA, SME incentives can be accessed through an EU/EEA-established SME. Both the regulatory consultancy and the non-EU/EEA-based company have to be assigned the SME status by the EMA SME office for the incentives to apply.

The fee incentives for SME apply to scientific services described in section 5.1.2 of the 'Explanatory note of fees payable to the European Medicines Agency'. Fee deferrals and conditional fee exemptions do not apply to scientific opinions issued pursuant to Article 58 of Regulation (EC) No 726/2004.

Reference

- Regulation (EC) No 2049/2005
- EMA website 'Supporting SMEs'
- Fees payable to the European Medicines Agency

11. What is the difference between scientific advice and a CHMP scientific opinion in collaboration with WHO?

Scientific advice is a service whereby an applicant / opinion holder can ask questions to the CHMP regarding pre- and post-marketing development of a medicinal product. This advice can be sought either on the initial development or any subsequent development, in order to raise scientific questions

pertaining to the scientific strategy chosen. The scientific advice provided allows the applicant / scientific opinion holder to take into consideration the CHMP views when generating data that later will become part of an application for or an update of a scientific opinion issued under Article 58.

Scientific opinion under Article 58 is an opinion adopted by the CHMP, in collaboration with WHO based on the evaluation of an application submitted to the EMA and containing data on the quality, safety and efficacy of the medicinal product; the CHMP opinion concludes on the benefit-risk balance of the medicinal product applied for.

12. How are pre-submission meetings conducted?

The pre-submission meetings are important steps in the product development and the regulatory process, and relate generally to the preparation of the submission of the application for a scientific opinion under Article 58. Successful pre-submission meetings should enable applicants to submit applications in conformity with the legal and regulatory requirements and be subsequently smoothly evaluated. These meetings will also enable applicants to establish contact with the EMA Members who will be closely involved in the evaluation procedure of their medicinal product. For more information, please see the EMA pre-authorisation procedural advice for users of the centralised procedure, 'How is a MAA pre-submission meeting conducted at the EMA'.

Reference

- 'Presubmission request form'

13. Do the requirements of the paediatric legislation apply to Article 58 applications?

The requirements of the paediatric legislation (Regulation (EC) No 1901/2006) do not apply to Article 58 applications. There is therefore no requirement for the Applicant to agree with the Agency on a paediatric investigation plan.

However, as most medicinal products falling under the framework of Article 58 could be used in children, applicants are encouraged to discuss the development of their products in the paediatric population within a scientific advice procedure. Scientific advice on paediatric questions is free of charge.

Reference

- Regulation (EC) No 1901/2006

14. What types of application can be submitted under Article 58?

The following types of application can be submitted under Article 58:

- full applications[1];

[1] As described in Article 8(3) of Directive 2001/83/EC.

- well-established use applications[2];
- fixed combination applications[3];
- informed consent applications[4];
- generic applications[5];
- hybrid applications[6];
- similar biological applications[7].

The type of application needs to be identified in the application form at the time of submission.

For further information on the different types of application and the related legal requirements see Notice to Applicants, Volume 2A, Chapter 1, section 5.

15. How are dossiers submitted?

For information on the submission requirements and the validation process, please refer to the EMA pre-authorisation procedural advice for users of the centralised procedure, Question 'How and to whom shall I submit my dossier?.

Applicants should use the specific application form for a scientific opinion under Article 58 available at the EMA webpage 'Article 58 applications: Regulatory and procedural guidance'.

16. When to submit my application under Article 58? Should I submit a letter of intent?

For information on when the application should be submitted and the dates of CHMP meetings please refer to the EMA pre-authorisation procedural advice for users of the centralised procedure, Question 'When to submit the Marketing Authorisation Application?'

17. Do I need an invented name for my medicinal product?

An invented name is not required for products applied for under Article 58 and therefore the Name Review Group will not be consulted.

Applicants are recommended to liaise with the relevant local authorities where the medicinal product is intended to be authorised in order to ensure compliance with the relevant national legislation.

[2] As described in Article 10a of Directive 2001/83/EC.
[3] As described in Article 10b of Directive 2001/83/EC.
[4] As described in Article 10c of Directive 2001/83/EC.
[5] As described in Article 10(1) of Directive 2001/83/EC.
[6] As described in Article 10(3) of Directive 2001/83/EC.
[7] As described in Article 10(4) of Directive 2001/83/EC.

18. Do I need to submit mock-ups and specimens?

Mock-ups or specimens do not need to be submitted *a priori* for products applied for under Article 58. Applicants should ensure the adequacy of the information on the labelling and the package leaflet, as well as its readability.

Applicants should liaise with the relevant local authorities where the medicinal product is intended to be authorised in order to ensure compliance with the relevant national legislation.

19. Do I have to submit samples together with my application?

Samples for testing the proposed medicinal product are not required at the time of submission of the application.

The CHMP may however request the testing of samples of the medicinal product and/or its ingredients during the assessment of the application.

In this case the (Co-)Rapporteur will specify a test protocol (type of samples, number of samples, number of batches, testing to be performed and methods and specifications to be used) and agree with the Agency which Official Medicines Control Laboratory (OMCL) or other laboratories designated for this purpose by a Member State will carry out the required testing.

Sampling and testing will be co-ordinated by the Agency in collaboration with the European Directorate for the Quality of Medicines and Healthcare (EDQM).

The results of the tests are reported to the Agency, (Co-)Rapporteur and the CHMP for consideration for the finalisation of the CHMP assessment report.

20. Do the QRD templates for product information have to be used?

It is recommended that the product information is submitted in line with the English QRD templates. Only the English product information will be reviewed in the Article 58 procedure.

Applicants should liaise with the relevant local authorities where the medicinal product is intended to be authorised in order to ensure compliance of the product information with the relevant national legislation.

References:

- EMA Homepage '[Quality Review of Documents]'

21. Do scientific opinions under Article 58 benefit from data or market protection/exclusivity?

Rules on data and market protections for EU marketing authorisations foreseen in Regulation (EC) No 726/2004 and Directive 2001/83/EC, as well as rules on market exclusivity foreseen in Regulation (EC) No 141/2000 do not apply to scientific opinions provided under Article 58.

22. Should ATC codes and international non-proprietary names agreed by WHO be used?

ATC codes and international non-proprietary names (INNs), when available, should be used in the Article 58 applications.

23. Can I submit a user testing of the Package Leaflet as part of the Article 58 application?

Submission of the results of a user testing of the Package Leaflet in the Article 58 applications is recommended to ensure the adequacy and the readability of the design and content of the package leaflet.

Applicants should liaise with the relevant local authorities where the medicinal product is intended to be authorised in order to ensure compliance of the package leaflet with the relevant national requirements.

24. What is the timetable for the validation and the evaluation of applications under Article 58?

The validation process and the evaluation procedure by the CHMP for Article 58 applications follows by analogy the same steps and timeframes as for the centralised marketing authorisation procedure. As the evaluation is conducted in partnership with the WHO, the WHO experts will provide input to the procedure. The WHO experts and observers from authorities of target countries nominated by WHO may also attend CHMP plenary and any other discussions on the products being assessed.

Details on the validation procedure can be found in the EMA pre-submission guidance Question 'How and to whom should I submit my dossier?' and Question 'How are initial Marketing Authorisation Applications validated at the EMA?'

Once the application is validated and provided the Rapporteurs confirmed the reception of the dossier, the EMA will start the procedure at the monthly starting date published on the EMA website.

The timetable prepared by the EMA in consultation with the (Co-)Rapporteur is adopted by the CHMP. The EMA ensures that the CHMP scientific opinion is given within 210 days.

The standard timetable for the evaluation of an application for a CHMP scientific opinion is below:

Day	Action
1	Start of the procedure
80	Receipt of the assessment reports from the Rapporteur and Co-Rapporteur by CHMP members and the EMA. EMA sends the assessment reports to the applicant, making it clear that they only set out the preliminary conclusions, that they are sent for information only and that they do not represent the position of the CHMP yet.
94	PRAC Rapporteur circulates the RMP assessment report, focusing on the prospective planning aspects: pharmacovigilance plan and risk minimisation measures, and

	proposed RMP list of questions (LoQ). EMA sends also the PRAC Rapporteur AR to the applicant.
100	(Co-)Rapporteurs, other PRAC and CHMP Committee members, WHO experts and EMA send comments (including peer reviewers).
101-104 (step exceptionally applicable)	PRAC adopts PRAC RMP assessment overview and PRAC Advice for D120 LoQ (PRAC discussion and adoption of advice during the 1st assessment phase is only envisaged for a minority of applications such as ATMP, PUMA or products assessed under accelerated assessment).
115	Receipt of draft list of questions (including the CHMP recommendation and scientific discussions) from the Rapporteur and Co-Rapporteur, as discussed with the peer reviewers, together with the PRAC RMP assessment overview and PRAC Advice, by CHMP members, WHO Experts as appropriate, and the EMA.
120	Adoption of the LoQ, overall conclusions and review of the scientific data by the CHMP. The EMA sends these to the applicants and WHO Experts, as appropriate. At the latest by Day 120, adoption by CHMP of request for GMP/GLP/GCP inspection, if necessary (Inspection procedure starts).

By analogy to the evaluation of centralised marketing authorisation applications, the same rules apply with regards the time allowed for applicants for the clock stop at D120 in order to respond to the list of questions and list of outstanding issues (EMEA/75401/2006 Rev. 2).

Responses are submitted by the applicant at day 121, including a revised summary of product characteristics (SmPC), labelling and Package Leaflet in English. The clock is restarted.

After receipt of the responses, CHMP adopts a timetable for the evaluation of the responses. The standard timetable is as follows:

Day	**Action**
157	Receipt of joint response assessment report from the CHMP (Co-)Rapporteurs and PRAC Rapporteur by CHMP, PRAC members and the EMA. EMA sends the joint assessment report to the applicant, WHO Experts, as appropriate, making it clear that it only sets out their preliminary conclusions, that it is sent for information only and that it does not represent the position of CHMP yet. Where applicable, inspection is carried out. EMA/QRD sub-group meeting for the review of English product Information with participation of the applicant (optional) around day 165.
166	PRAC adopts PRAC assessment overview and PRAC Advice for D180 LoOI.
170	Deadline for comments on joint assessment report from CHMP members and WHO Experts as appropriate. The CHMP Rapporteur will integrate the various contributions and views in the draft List of outstanding issues.
180	CHMP discussion and decision on the need for adoption of a LoOI and/or on whether the applicant will need to attend an oral explanation. Submission of the final inspection report to EMA, Rapporteur and Co-Rapporteur by the inspections team, if applicable. CHMP adopts the LoOI as well as the overall conclusions and review of the scientific data to be sent to the Applicant by the EMA.
181	Clock is restarted with submission of responses or oral explanation. Oral explanation takes place (if needed).

194	The CHMP (Co)-Rapporteurs/ PRAC Rapporteur assess the applicant's responses including the RMP aspects in a joint assessment report. A PRAC discussion is not foreseen at this stage.
200	PRAC and CHMP Committee members, WHO experts as appropriate and EMA send comments on the assessment report.
204	The updated AR is circulated to the PRAC and CHMP Committee members, WHO experts and EMA.
By 210	Adoption of CHMP scientific opinion and assessment report.

The above timetable will be reduced in case of application under accelerated assessment. Please refer to the EMA pre-submission guidance Question 'Is my product eligible for an accelerated Assessment?' for further details.

After adoption by CHMP, the scientific opinion and its annexes are sent to the relevant stakeholders and a public assessment report on a scientific opinion in co-operation with WHO (EPAR) is prepared within 2 months following the adoption of the scientific opinion under Article 58. This public assessment report is published on the EMA website.

25. Can I ask for a re-examination in case of a negative scientific opinion?

Applicants have the possibility of requesting a re-examination of the CHMP scientific opinion under Article 58.

Within 15 days of receipt of the scientific opinion, the applicant should inform the EMA of its intention to request a re-examination and submit the grounds for the request for re-examination within 60 days of receipt of the opinion. The applicant should also mention if he wishes to appear for an oral explanation.

Within 60 days from the receipt of the grounds for the request for re-examination, the CHMP will evaluate the arguments presented by the applicant and will adopt a final scientific opinion. If necessary, an oral explanation can be held within this 60-day timeframe.

26. When and how are the (Co-)Rapporteurs appointed?

Applicants are requested to notify the EMA of their intent to submit and request assignment of (Co-) Rapporteurs 7 months prior to the intended submission date. The (Co-) Rapporteurs appointment procedure will not be initiated prior to this notification of intended submission date.

For details on the procedure to nominate (Co-)Rapporteurs, please refer to the EMA pre-authorisation procedural advice for users of the centralised procedure, Question 'What is the procedure for appointment of CHMP/PRAC/CAT Rapporteurs/Co-Rapporteurs and their assessment teams?'.

References:

- Procedural Advice on CHMP/CAT/PRAC Rapporteur/Co-rapporteur appointment principles, objective criteria and methodology in accordance with Article 62 (1) of Regulation (EC) NO 726/2004 (EMA/151751/2010)
- CHMP Rules of Procedure (EMEA/CHMP/45110/2007)

27. How are experts appointed and how are they involved?

For applications evaluated under Article 58, experts and observers nominated by WHO can be involved in the evaluation. The Agency informs applicants of the WHO experts and observers that are appointed for their application at the start of the procedure.

WHO experts and experts nominated by WHO from target countries act as scientific expert reviewers to the rapporteurs' assessment reports and provide specific expertise and input as appropriate. Their precise tasks and responsibilities in a particular procedure will depend on the specific product, therapeutic area and their areas of expertise. They may, for instance, be asked to comment on assessment reports or provide specific expertise at CHMP or other meetings. Observers nominated by WHO can also attend CHMP and other meetings and may be invited to provide appropriate input. Experts and observers have no voting rights at the CHMP.

All nominated experts must carry out their tasks and responsibilities in accordance with EMA policies on confidentiality and conflicts of interest (see EMA Code of Conduct). Prior to their appointment and participation in meetings, all experts are obliged to submit a completed and signed nomination form, a *curriculum vitae*, a public declaration of interests and confidentiality undertaking form. In addition, experts can only participate in discussions on products to an extent that is defined by their individual level of risk, in accordance with the EMA policy and procedure on the handling of conflicts of interest.

Applicants are responsible for sending a copy of modules 1 and 2 of the dossier to WHO experts and observers if they have been appointed, at the start of the procedure. They also need to send them a copy of any other relevant documentation that they produce during the procedure, such as responses to lists of questions or lists of outstanding issues. The EMA is responsible for forwarding the relevant documents circulated and adopted during the evaluation procedure to the appointed WHO experts and observers.

References:

- The EMA Code of Conduct

28. Can the evaluation of a medicinal product under Article 58 be accelerated?

Yes, the evaluation of a medicinal product under Article 58 can be accelerated upon request of the applicant. The request is assessed by the CHMP in consultation with the WHO if appropriate. Applicants should provide justification and rationale for any requests for accelerated assessment.

The timing and the documentation referred in the EMA pre-authorisation procedural advice for users of the centralised procedure Question 'is my product eligible for an accelerated assessment?' should be submitted. The applicant should justify that the medicinal product would offer a major interest from the point of view of public health in the targeted countries where it is intended to be authorised.

29. Is it possible to claim a scientific opinion under Article 58 subject to specific obligations?

The frameworks of conditional marketing authorisation or a marketing authorisation under exceptional circumstances can be applied by analogy to scientific opinions under Article 58. The applicant should submit as part of the application, a proposal for the appropriate post-authorisations measures (so-called 'specific obligations') together with a justification to its claim.

The CHMP may propose on its own motion such framework to the applicant.

The following guidelines should be taken into consideration:

- Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to article 14 (8) of regulation (EC) no 726/2004
- Guideline on the scientific application and the practical arrangements necessary to implement commission regulation (EC) no 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of regulation (EC) no 726/2004

30. What is the fee for an application under Article 58?

The fees applied for the assessment of centralised marketing authorisation applications, post-opinion services and annual fees apply by analogy to applications under Article 58.

Small and medium-sized enterprises may benefit from some incentives in relation to scientific opinions pursuant to Article 58 of Regulation (EC) No 726/2004 (see question 10).

Applicants have also the possibility to request a total or partial waiver of the fee, which may be granted by the EMA's Executive Director after consultation of the CHMP. Requests for waivers should be sent to the Executive Director with appropriate justification as early as possible, but not later than three months prior to the anticipated date of submission of the application for scientific advice.

For more information, please refer to the EMA pre-authorisation procedural advice for users of the centralised procedure Question 'What fee do I have to pay and how is the appropriate fee for my application calculated?'.

The EMA contacts point for queries on Fees, Procedures or Application numbers, are:
Product and Application Business Support (PA-BUS) or e-mail address: pa-bus@ema.europa.eu

References:

- Fees payable to the European Medicines Agency

31. Is a pharmacovigilance system and risk management plan needed?

In principle, the same requirements for pharmacovigilance systems and risk management plans (RMPs) apply for applications under Article 58 as for centrally authorised products and it has to be adapted to the patients and to the health systems of the countries where the medicinal product is intended to be authorised.

Whilst a RMP should be submitted for all applications under Article 58, certain parts or modules of the RMP may be omitted when justified. Applicants are encouraged to contact the EMA prior to submitting an application under Article 58 to discuss RMP related questions.

At any stage, but in particular during the pre-authorisation phase, an applicant/holder may request advice on the development or the appropriate pharmacovigilance activities/risk minimisation measures in relation with an Article 58 scientific opinion through the scientific advice procedure.

Besides, the summary of the pharmacovigilance system needs to be submitted at the time of application in module 1.8.1 and the proposed RMP should be submitted in module 1.8.2.

The scientific opinion holder, should inform the EMA of any deviation to the submitted documentation, and should provide the reason for such deviations. The CHMP, in collaboration with the WHO, may revise its opinion based on this information.

References:

- Good Pharmacovigilance Practices for medicinal products for human use

32. Can I submit an environmental risk assessment in the target markets?

The submission of an environmental risk assessment (ERA) is recommended for applications under Article 58. In case an ERA is not submitted, an appropriate justification should be included in the dossier.

Applicants are recommended to liaise with the relevant local authorities where the medicinal product is intended to be authorised in order to ensure that the documentation complies with the relevant national legislation.

Reference

- Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00).

33. What information should be provided on manufacturers in an application under Article 58?

In the notification of intention to submit an application under Article 58, applicants should mention the names, contact points, addresses and activities of the proposed manufacturers of the active substance(s) ('drug substance') and finished product (drug product'). The sequence of all different manufacturing sites involved should be clearly described in a flowchart.

Application Form:

All sites involved in the production of the finished product and of the active substance(s) should be described (name and detailed address, including building reference) in section 2.5 of the application form, together with a description of the steps/activities performed at each site. This information must be consistent with the Module 3. It should include:

2.5.2: any site or contract laboratory used for quality control testing the finished product, including in-process testing sites.

2.5.2: any site responsible for the manufacture of the medicinal product manufacture, including manufacturing sites of any diluent/solvent presented in a separate container but forming part of the medicinal product, immediate and outer packaging.

2.5.3: any site involved in the manufacturing process of each source of active substance, including quality control / in-process testing sites. For biotechnology products, all sites of storage of master and working cell bank and preparation of working cell banks when relevant should be included.

For third country manufacturer(s), information about any previous GMP inspection (with, a copy of the GMP certificate if available) and/or any planned GMP inspection(s) should be provided, including details of the inspection dates, product category inspected and the name(s) of the inspecting competent authorities. Please also include WHO Pre-Qualification inspections, if available).

Documents to be attached to the application form:

For all sites in the EEA, other than active substance manufacturers, copies of the 'Manufacturing Authorisation' or the EudraGMDP manufacturing authorisation reference number should be provided.

For all sites, other than active substance manufacturers, located in third countries, a document equivalent of manufacturing authorisation issued by the local competent authorities should be provided. If available, the latest GMP certificate or EudraGMDP certificate reference number should be provided.

A flowchart describing all the main steps involved in the manufacture of the active substance and finished product.

A document (C.V.) identifying the contact person responsible for product defects and recalls including its contact details.

Product defects and recalls:

The scientific opinion holder should report forthwith to the competent authorities of the countries where the product is authorised and inform the EMA about any defect in a medicinal product that could result in a recall or abnormal restriction in supply, together with the corrective action(s) proposed. Depending on the quality issue(s), the CHMP may revise the scientific opinion.

34. Do products need to be tested by an Official Medicines Control Laboratory before they are released for sale?

The CHMP may recommend that certain products (such as vaccines, immunological products or medicinal products derived from human blood or human plasma) need testing of individual batches performed by an independent control laboratory before release on the relevant market(s). Therefore, the scientific opinion holder could be requested to submit samples from each batch of the bulk or medicinal product to an official medicines control laboratory (OMCL). A batch of a medicinal product can be placed on the relevant market(s) once the OMCL has examined the batch in question and declared it to be compliant with the approved specifications by issuing a certificate of batch compliance.

The CHMP provides as part of the scientific opinion a list of the tests to be carried out by an OMCL.

OMCLs located in the EU are appointed by the European Directorate for the Quality of Medicines (EDQM). The EU OMCL should complete testing within 60 days after they have received the sample. If

the product is compliant, the EDQM provides a certificate of batch compliance to the applicant, who may then provide it to the local competent authorities where the medicinal product is authorised.

References

- European Directorate for the Quality of Medicines

35. When is a good manufacturing practice, a good laboratory practice or good clinical practice inspection needed? How are inspections carried out?

The same principles apply for good manufacturing practice (GMP), good laboratory practice (GLP) and good clinical practice (GCP) inspections for evaluations under Article 58 as for the evaluation of a centrally medicinal product.

For details, see EMA website 'inspections'.

For applications where the manufacturing site of the drug product is located inside the EEA, the Supervisory Authority is responsible for the inspection. For applications where the manufacturer of the product is located outside the EEA, a Competent Authority within the EEA will be nominated.

In case of request of accelerated assessment, the applicant should to submit specific information in order to anticipate and integrate routine GCP and pre-approval GMP inspections into the accelerated assessment procedure. Applicants should refer to the EMA pre-authorisation guidance 'Is my product eligible for an accelerated Assessment?' for further details on the information to be provided and the related templates.

36. What is the fee for an inspection?

The same fee as for inspection in the context of a centralised marketing authorisation application is charged.

For inspections outside the European Union, the applicant is also required to pay the travel and accommodation expenses for the inspectors and any experts or Rapporteurs involved. These expenses are paid directly by the applicant to the inspectors' authorities.

Fee incentives apply to SMEs established in the EU/EEA, in particular for inspection - please refer to question 10.

For more information on inspection fees, please refer to Fees payable to the European Medicines Agency.

References:

- Fees payable to the European Medicines Agency

37. Can I submit active substance master file(s) (ASMF), vaccine antigen master file (VAMF) or plasma master file (PMF) for an application under Article 58?

For active substances that may be subject to an ASMF, applicants may use this possibility in the context of an application under Article 58. Applicants should include information on their intention to present the equivalent of an EU active substance master file (ASMF) when they send their notification of intention to submit an application under Article 58.

Applicants should refer to the Guideline on Active Substance Master File Procedure (CHMP/QWP/227/02) for and the content requirements and the procedure to follow. If an ASMF already exists, the applicant should ensure that the active ingredient manufacturer's (AIM's) restricted part of the ASMF is submitted by the AIM at the same time as the main application.

Please note that the applicant should include a commitment to inform the EMA of any changes in the ASMF either as a separate letter included in Annex 5.11 or within the letter of access provided in Annex 5.11 of the application form.

Additional information can be found in the EMA Pre-submission guidance Question 'How should I submit an active substance master file (ASMF)?' and 'Practical Guidance on the use of the eCTD format for ASMF for Active Substance Master File Holders and Marketing Authorisation Holders'.

The concept of the ASMF does not apply to blood-derived medicinal products and vaccine antigens. In this context, the manufacturer can submit a PMF or a VAMF. If an applicant intends to use existing vaccine antigen master file (VAMF) or plasma master file (PMF) certificates in an application under Article 58, he will need to provide the valid VAMF or PMF certificate of compliance with European Union legislation and accompanying evaluation reports together with the respective VAMF or PMF data.

References:

- Guideline on Active Substance Master File Procedure (CHMP/QWP/227/02)

38. What information is needed for medicinal products that contain or use material of animal or human origin in the manufacturing process?

If a medicinal product contains material of animal or human origin or uses it in its manufacture, the applicant should comply with the Part I Module 3.2 (9) "Content: basis and principle" of the Annex I to Directive 2001/83/EC. This requires the applicant to demonstrate that the medicinal product is manufactured in accordance with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

This can be achieved by either of the following means:

- submitting certificates of suitability from the European Directorate for the Quality of Medicines (EDQM) in Annex 5.13 of the application form;
- inclusion of scientific data in Module 3.2 of the dossier to establish compliance, together with a review of these data in Module 2.3 (expert reports).

For all applications, table A on Materials of animal origin covered by the Notice for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products should be completed and included in Module 3.2.R.

For material from animals that is not covered by the Notice for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products and annex I of Directive 2001/83/EC or for materials of ruminant origin used in the establishment of existing master cell banks, applicants are requested to complete table B on 'Other materials of animal origin', and include it in Module 3.2.R.

If an application relates to a medicinal product that contains or uses material of human origin in its manufacture, applicants are requested to complete table C on albumin and other human tissue derived materials and include it in Module 3.2.R.

For adventitious agents, information assessing the risk with respect to potential contamination with adventitious agents, whether they are non-viral or viral, as laid down in relevant guidelines as well as in relevant general monograph and general chapter of the European Pharmacopoeia, shall be provided.

References:

- Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products (EMEA/410/01)
- European Medicines Agency's scientific guidelines on biological medicinal products

39. Is a Commission Decision granted after adoption of a scientific opinion under Article 58?

There is no Commission Decision granted following the adoption of an opinion under Article 58.

This opinion under Article 58 is transmitted to the scientific opinion holder and to the WHO.

40. What is published following a scientific opinion under Article 58?

Within 2 months following the adoption of the scientific opinion under Article 58, a public assessment report, similar to the assessment report for centrally authorised medicinal products, is published.

The public assessment report for Article 58 reflects the scientific conclusions reached by the CHMP at the end of the evaluation process with redaction of commercially confidential information.

In addition to the assessment report, EMA publishes a lay-language summary for the public, the product information and a list of all authorised presentations. These documents are available on the medicines webpage, which is updated throughout the life-cycle of the product.

An assessment report and a questions-and-answers document are published following the withdrawal of an application for a scientific opinion or following a negative scientific opinion. More details can be found on the EMA website on Question 'what we publish on medicines and when?'.

All documents related to Article 58 are published in English only.

41. Can the EMA certify scientific opinions under Article 58?

The Agency can delivers certificates for medicinal products which have been subject to an opinion pursuant to Article 58.

The European Medicines Agency issues certificates within 10 working days (standard procedure) or within 2 working days (urgent procedure) following receipt of a valid application form.

For more information regarding certificates, in particular on the practical details to make a request, please see the EMA website on 'Certificates of medicinal products'.

42. What information do I need to submit after the opinion?

The scientific opinion holder shall keep the scientific opinion up-to-date and submit any corresponding change to the EMA. Any information that may have an impact on the benefit-risk balance of the medicinal product shall be submitted to the EMA forthwith. The holder must also take into account any technical and scientific progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. Any amendment to the opinion need to be assessed by the EMA in collaboration with the WHO via **variation applications**. By analogy to centralised marketing authorisations, the same procedural elements (notably the categorisation of variations) and the data requirements to support such applications, apply. For further details, the scientific opinion holder should refer to the EMA post-authorisation guidance. Applicants should use the specific application forms available at the EMA webpage 'Article 58 applications: Regulatory and procedural guidance'.

In particular cases, the Scientific Opinion Holder may be requested to submit Post-Authorisation Measures (PAM) to the Agency, the submission must be in accordance with the corresponding procedural details laid down in the EMA website – Post-Authorisation Measures.

In the framework of their confidentiality arrangement, the EMA and WHO can exchange any information relating to medicinal products evaluated under the Article 58 procedure. The EMA will contact the WHO for any relevant information related to the scientific opinion under Article 58.

It is reminded that the post-authorisation activities related to the scientific opinion under Article 58 are without prejudice to the scientific opinion holder's obligations; they shall also ensure compliance with the relevant national legislation where the medicinal product is authorised.

43. What are the pharmacovigilance requirements in relation with the Article 58 Scientific Opinion?

The following pharmacovigilance obligations related to the Article 58 opinions do not substitute to the requirements of the national countries (e.g. in terms of reporting of adverse reactions) where a marketing authorisation has been granted and for which the scientific opinion holder shall ensure compliance with the relevant national legislation where the medicinal product is authorised.

With regards to its pharmacovigilance requirements at the level of the EMA:

- All reported **serious adverse reactions** should be recorded by the scientific opinion holder and submitted to the EMA within the time frames and format stated in the Module VI 'Management and reporting of adverse reactions to medicinal products' of the Guideline on good pharmacovigilance practices (GVP) and in the other documents available on the EMA Website – EudraVigilance.
- **Periodic safety update reports** (PSURs) for the concerned medicinal products should be submitted in accordance with the frequency stated in the scientific opinion under Article 58. The format of the PSUR shall follow the structure described in the Commission implementing Regulation (EU) No 520/2012. By analogy, the same content of the PSUR and the related submission modalities as for centralised marketing authorisations apply. Further details can be found in Module VII 'Periodic safety update report' of the Guideline on good pharmacovigilance practices (GVP) and on the EMA Website – PSUR, in particular the 'Questions and Answers on PSURs'.
- To perform signal detection on any data sources available to them (e.g. opinion holder's safety database, scientific literature) related to their medicinal products. Should any information that may affect the benefit-risk balance of the medicinal product be raised, the holder should inform the Agency forthwith. By analogy to the centralised marketing authorisations, the holder should follow the requirements for the management of safety signals as described in Module IX 'Signal management of the Guideline on good pharmacovigilance practices (GVP) and on the EMA website – Signal management, in particular the 'Questions and Answers on signal management'.
  The documentation from the CIOMS Working Group VIII on Application of Signal Detection in Pharmacovigilance (CIOMS VIII) can be found on the Council for International Organizations of Medical Sciences website.

The Scientific Opinion Holder may be required to submit to the Agency Post-Authorisation Measures (PAM), such as study protocols. The submission must be in accordance with the corresponding procedural details laid down in the EMA website – Post-Authorisation Measures.

In case of new information that may affect the benefit-risk balance of the medicinal product, the CHMP in consultation with the WHO can revise the scientific opinion on its own initiative.

In the framework of their confidentiality arrangement, the EMA and WHO can exchange any information relating to medicinal products evaluated under the Article 58 procedure. The EMA will contact the WHO for any relevant information related to the scientific opinion under Article 58.

It is reminded that the post-authorisation activities related to the scientific opinion under Article 58 are without prejudice to the Scientific Opinion Holder's obligations; they shall also ensure compliance with the relevant national legislation where the medicinal product is authorised.

References

- EMA – Post-authorisation guidance
- EMA - Pharmacovigilance
- Good Pharmacovigilance Practices for medicinal products for human use

44. What to do in case of product defects or batch recalls?

The scientific opinion holder shall report forthwith any product defect, together with the corrective actions proposed, which may result in significant restriction in supply of the medicinal product or in a batch recall to:

- the competent authorities of the countries where the product is authorised, in accordance with the relevant national legislation.
- the EMA.

Depending on the nature of the issue, CHMP may revise its opinion in collaboration with WHO.

45. Can the scientific opinion under Article 58 be transferred to another holder?

The scientific opinion under Article 58 can be transferred to another scientific opinion holder.

The current (transferor) and the next (transferee) scientific opinion holders need to submit to the EMA a signed declaration (see cover letter template) stating:

- The name of the medicinal product concerned.
- The identification (name, address, contact person at opinion holder's address, telephone number and email address) of the transferor and the transferee.
- A document certifying that the complete and up-to-date file concerning the medicinal product or a copy of this file has been made available to or has been transferred to the transferee.
- If applicable, the date on which the transferor and the transferee finalise the transitional organisational arrangements and the transferee takes over all responsibilities. This is referred to as the implementation date. The duration of this transitional period should be proportionate to the organisational activities that need to be performed by the transferor and transferee and should not exceed 6 months. The activities performed by the transferor during the transitional period should be described.

The transferee needs to submit a signed declaration (attachment 1) stating:

- The name and contact details of the person authorised for communication with EMA.
- The name and contact details of the person responsible for quality issues.

The transferee and the responsible for pharmacovigilance need to submit a signed declaration (attachment 2) stating:

- The name and contact details of the responsible for pharmacovigilance.
- That the transferee has at his disposal a qualified person responsible for pharmacovigilance and the necessary means to fulfil the relevant tasks and responsibilities listed in Title IX of Directive 2001/83/EC by analogy.

Where applicable, an update of the product information and of the summary of the pharmacovigilance system should be submitted in Modules 1.3.1 and 1.8.1

For further details on the procedure, please refer by analogy to Questions 'How and to whom shall I submit my transfer of marketing-authorisation application?' and 'How shall my transfer-of-marketing-authorisation application be handled (timetable)?'.

The transferor and transferee are recommended to liaise with the EMA in advance of the submission to streamline the transfer procedure.

46. What should be done where the holder does not intend to maintain the scientific opinion under Article 58?

In case the holder intends to not maintain the scientific opinion under Article 58, the holder should send a letter to the EMA notifying its intention to not update anymore the scientific opinion. The holder should include the following information:

- background reason(s);
- countries where a MA were granted based on the Article 58 opinion and where the product is currently authorised/marketed and estimate for the remaining products to be on the market (last batch released and expiry date of last batch);
- declaration that the applicant will ensure post-authorisation activities related to the medicinal product administered to patients and the remaining medicinal product on the market if there is no batch recall (e.g. ADR reporting, quality defects reporting)
- list and status of the remaining post-authorisation measures, as well as the ongoing procedures (PSUR, variations…).
- details of the communication plan to inform the public health authorities and other relevant public health actors, as well as the public and healthcare professionals of the concerned countries;
- information on the therapeutic alternatives available, if appropriate

The EMA will update accordingly the product-webpage of the medicinal product.

The above is without prejudice to the scientific opinion holder's duty to inform appropriately the countries where a marketing authorisation was granted based on the scientific opinion under Article 58 and to ensure compliance with relevant national legislation.

47. How long is the Article 58 opinion valid?

The scientific opinion under Article 58 remains valid unless otherwise stated by the Agency on the relevant EMA webpage.