



European Medicines Agency
Evaluation of Medicines for Human Use

London, 1 April 2009
Doc.Ref. EMEA/534107/2008

PRE- and POST- “ARTICLE 58” SCIENTIFIC OPINIONS
PROCEDURAL ADVICE FOR USERS

**EMEA PROCEDURAL ADVICE
ON
MEDICINAL PRODUCTS INTENDED EXCLUSIVELY FOR
MARKETS OUTSIDE THE COMMUNITY UNDER ARTICLE
58 OF REGULATION (EC) NO 726/2004 IN THE CONTEXT
OF CO-OPERATION WITH THE WORLD HEALTH
ORGANIZATION (WHO)**

Comments should be provided using [this template](#) to article58@emea.europa.eu or Fax +44 20 75 23 70 51

EMEA PROCEDURAL ADVICE ON MEDICINAL PRODUCTS INTENDED EXCLUSIVELY FOR MARKETS OUTSIDE THE COMMUNITY UNDER ARTICLE 58 OF REGULATION (EC) NO 726/2004 IN THE CONTEXT OF CO-OPERATION WITH THE WORLD HEALTH ORGANIZATION (WHO)

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 EMEA's position on issues that are typically addressed in pre-submission meetings.

The EMEA emphasises the importance of pre-submission meetings with applicants. These meetings are a vital opportunity for applicants to obtain procedural, regulatory and legal advice from the EMEA. 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 EMEA staff who will be involved with the application as it proceeds.

For further information on the contents of this document or in case the applicants would like to contact WHO prior to the submission of an eligibility request, a request for scientific advice or an application for Article 58 of Regulation (EC) No 726/2004 to the EMEA, please send an e-mail to article58@emea.europa.eu.

For information on pre-submission meetings, please contact:

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Instructions for users:

To obtain the information on a certain topic, simply 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.

For clarification on any of the topics below or to apply for a pre-submission meeting, please use the Pre-submission Meeting for Article 58 of Regulation (EC) 726/2004 procedure Request Form marking which topics you would like to be addressed by the EMEA.

When you have completed the request form, please return it by mail or e-mail.

Note:

This document has been produced for guidance only and should be read **in conjunction** with the [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of co-operation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community \(EMEA/CHMP/5579/04\)](#).

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1. 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 Community**. The Article responds to the need to protect public health and to give scientific assistance in the context of co-operation with the World Health Organization (WHO), whilst allowing rapid access to medicinal products in countries outside the Community.

Eligible products include medicines that are intended for the prevention or treatment of diseases of major public interest. They include but are not limited to¹:

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

Applicants need to request eligibility for evaluation under Article 58 for a medicinal product before submitting an application. The EMEA’s Committee for Medicinal Products for Human Use (CHMP), evaluates data on the quality, safety and efficacy of the product contained in the application in collaboration with the WHO, before issuing a scientific opinion concluding on the benefit-risk ratio of the product.

References:

- [Regulation \(EC\) No 726/2004 of the European Parliament and of the Council](#)
- [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of co-operation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community](#)
- [Notice to Applicants, Volume 2A, Chapter 4](#)

2. How are requests for eligibility submitted?

The eligibility request which is free of charge is made using the eligibility form, sent to the following address: article58@emea.europa.eu.

This request 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 draft summary of product characteristics (SPC) or a product profile;
- a justification for the product’s eligibility for evaluation under Article 58. It is recommended that any available epidemiological data on the disease, data on disease burden and a summary of any efficacy or safety data also be submitted;
- a statement that the applicant does not intend to market the medicinal product in the European Economic Area (EEA);
- the proposed classification for the supply of the medicinal product, i.e. not subject to medical prescription or subject to medical prescription (renewable or non-renewable);
- a list of the countries in which the applicant intends to market the product;

¹ Clarification should be sought from the EMEA if necessary.

- a declaration from the applicant agreeing on communication between the EMEA and the WHO using the template “Agreement between EMEA and the Applicant”;
- a justification or rationale for a shorter evaluation review, if appropriate.

Confirmation of eligibility is needed before an applicant submits an application for a CHMP scientific opinion. The request should be submitted at least seven months prior to submission of the application. Confirmation is also recommended in advance of a request for scientific advice on the development of the product.

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

References:

- [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of co-operation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community](#)

3. How is eligibility assessed?

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

Once the EMEA have received the eligibility request by the applicant it is sent to WHO. Within two months of the submission of the eligibility request, the WHO forwards its position to the EMEA. The EMEA’s Committee for Medicinal Products for Human Use (CHMP) then examines the eligibility for evaluation under Article 58, confirming or not confirming the WHO’s position as appropriate. The outcome of the assessment is sent to the applicant after the next CHMP plenary meeting. The applicant also receives the WHO “eligibility feedback” letter and the EMEA/CHMP eligibility letter. If eligibility is refused, the reasons for this are stated.

If a large number of applications is received by the EMEA, WHO can prioritise applications, with the highest priority applications being dealt with first.

4. How long is eligibility valid for?

The eligibility of a medicinal product for evaluation under Article 58 is not expected to change once agreed upon, because it is based on the need to protect public health in developing countries, which is unlikely to change between the eligibility request and the submission of the application.

In case there is a long delay between the eligibility request, i.e. more than 2-3 years, and the submission the applicant may be requested to resubmit the eligibility request at the time of notification of intention to submit. Further, where the epidemiological situation or environment changes, the applicant is strongly advised to request reconfirmation of eligibility by the EMEA and WHO.

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

Applicants or their contact points must be established in the EEA, i.e. a Member State of the European Union (EU), Norway, Iceland or Liechtenstein. Evidence to support this must be provided both at the time of submitting an eligibility request and at the time of submission of the application (in Annex 5.3 of the application form).

References:

- [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of co-operation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community](#)

6. Can applicants ask for scientific advice?

Yes, Article 58(2) makes provision for scientific advice on medicinal products intended to be marketed exclusively outside the Community. Scientific advice is given by the CHMP's Scientific Advice Working Party (SAWP) in response to scientific questions concerning quality, non-clinical and clinical aspects. 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.

If an applicant is considering seeking scientific advice ahead of an application for a CHMP scientific opinion, it is recommended that the eligibility request is made at least four months prior to the application for scientific advice. However, if there is a long delay between the request for scientific advice and the application for a CHMP scientific opinion, i.e. more than 2-3 years, the applicant may be requested to resubmit the eligibility request at the time of notification of intention to submit.

The existing procedural guidance on scientific advice for medicinal products intended for use within the EU also applies to scientific advice on possible future applications for a CHMP scientific opinion under Article 58.

The timeframe for a standard scientific advice procedure is 40 days. This is extended to 70 days if there is a need for a face-to-face meeting with the applicant. Further information and a template for request are available on the EMEA website [‘Scientific Advice and Protocol Assistance’](#).

7. How much does scientific advice cost?

The same fees for scientific advice apply for products to be evaluated under Article 58 as for the centralised procedure.

In exceptional cases, a total or partial waiver of the fee may be granted by the EMEA'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.

References:

- [‘New framework for Scientific Advice & Protocol Assistance’ \(EMEA/267187/2005/ Rev. 1\)](#)

8. 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 EMEA has set up an ‘SME office’, which offers financial and administrative assistance to SMEs. Details of how to register as an SME with the Agency are available on the EMEA's website.

Although there are no fee reductions for Article 58 procedures *per se* for SMEs, there is a 90% fee reduction available to SMEs seeking scientific advice from the Agency. Applicants may also request regulatory assistance from the SME office.

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

Scientific advice is a service whereby an applicant or opinion holder can ask questions to the CHMP regarding the development of a medicinal product. This advice can be sought either before or after the opinion, in order to confirm whether the CHMP agrees with the scientific strategy chosen. The outcome of a request for scientific advice allows the applicant or opinion holder to take the views of the CHMP into account when generating data that later will become part of an application for an opinion or an update to an existing opinion.

An **Article 58 CHMP scientific opinion** is an opinion issued by the CHMP, the scientific committee of the EMEA, in collaboration with WHO. This opinion is based on the evaluation of an application containing data on the quality, safety and efficacy of the product, and concludes on the benefit-risk ratio of the product.

10. How are pre-submission meetings conducted?

Pre-submission meetings take place at the EMEA. They allow applicants to obtain procedural, regulatory and legal advice from the EMEA so that they can submit applications that conform with legal and regulatory requirements and that can be validated speedily. Pre-submission meetings also enable applicants to establish contact with the EMEA staff who will be involved with the application as it proceeds.

For more information, please see question 31 of the EMEA Pre-Submission Procedural Advice, [‘EMEA Pre-Submission Flow-chart’](#).

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

The requirements of the paediatric legislation (Regulation (EC) No 1901/2006 as amended) do not apply to Article 58 applications. These requirements only apply to medicinal products authorised in the Community or intended to be authorised in the Community. There is therefore no requirement to provide results in accordance with agreed paediatric investigation plans (PIPs). 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 these products for the paediatric population in a scientific advice procedure. Scientific advice on paediatric questions is free of charge.

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

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

- full complete (or full/ mixed) applications¹;
- well-established use applications²;
- new fixed combination applications³;
- informed consent applications⁴;
- generic applications⁵;
- hybrid applications⁶;
- similar biological applications⁷.

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

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

² As described in Article 10(a) of Directive 2001/83/EC.

³ As described in Article 10(b) of Directive 2001/83/EC.

⁴ As described in Article 10(c) 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.

For further information on the different types of application see [Notice to Applicants, Volume 2A, Chapter 1, section 5](#).

13. How are dossiers submitted?

For information on how to submit a dossier, please see question 23 of the EMEA Pre-Submission Procedural Advice '[How and to whom shall I submit my dossier? – How many paper copies? – Names and addresses of CHMP members](#)'.

For evaluations under Article 58, applicants are also responsible for sending a copy of modules 1 and 2 of the dossier to any WHO experts and observers appointed at the start of the procedure. They also need to send a copy of any other relevant documentation produced during the procedure, such as responses to lists of questions or lists of outstanding issues.

It is strongly recommended that dossiers be submitted electronically if possible. Please see question 24 of the EMEA Pre-Submission Procedural Advice '[Can I submit electronic copies of my dossier?](#)' For the latest information regarding e-submission please see [the e-submission webpage](#).

For information on when the application should be submitted and the [dates of CHMP meetings](#) please see question 25 of the EMEA Pre-Submission Procedural Advice '[When to submit the Marketing Authorisation Application?](#)'

14. What format should dossiers be in?

The Common Technical Document (CTD) format is preferred. The old NTA format is acceptable, provided that the applicant supplies appropriate justification for its use.

For information on the CTD format see [Notice to Applicants Volume 2B](#).

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

In principle, invented names are not required for “Article 58” medicinal products as the medicinal is exclusively intended to be used outside the Community.

References:

- [‘Guideline on the acceptability of names for human medicinal products processed through the centralised procedure’ \(CPMP/328/98, Revision 5\)](#)
- [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of co-operation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community](#)

16. In which languages should the product information, mock-ups and specimens be submitted in an application?

The product information should be submitted in English only, as electronic copies. No mock-ups or specimens need to be submitted for products evaluated under Article 58, as they are intended exclusively for markets outside the Community.

17. 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, in order to ensure standardisation in terms of headings. However, since the product is intended to be used by patients in countries where QRD requirements are not enforced, applicants can deviate from these templates. In this case, they should submit an edited QRD template with tracked changes, together with a justification for the deviations proposed.

References:

- EMEA Homepage “[Quality Review of Documents](#)”

18. Do scientific opinions benefit from data or market exclusivity?

Scientific opinions under Article 58 are not followed by an EU Commission Decision, the EC incentives such as data or market exclusivity do therefore not apply.

19. Do ATC codes and international non-proprietary names agreed by WHO have to be used?

The use of ATC codes and international non-proprietary names (INNs) agreed by WHO is highly recommended, but no legal requirement.

20. Is user testing of the Package Leaflet needed?

User testing of the Package Leaflet is not mandatory because the product is to be marketed outside the European Union. However, applicants are encouraged to carry out user testing.

21. What is the timetable for the evaluation of applications?

The evaluation procedure follows the same steps and timeframe as the centralised procedure. As the evaluation is a partnership between the EMEA and WHO, WHO experts provide input to the procedure. Observers from WHO and authorities of developing countries recommended by the WHO may also attend CHMP plenary discussions on products being assessed (see question 23).

The procedure starts once the application has been validated and the Rapporteur and Co-Rapporteur have confirmed that they have received the dossier and any additional information requested during the validation phase. The timetable for an individual product’s evaluation is prepared by the EMEA in consultation with the Rapporteur and Co-Rapporteur and is adopted by the CHMP. The EMEA 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 EMEA. The EMEA 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 yet represent the position of the CHMP.
100	Receipt of comments on the assessment reports from CHMP members (including peer reviewers) by the Rapporteur, Co-Rapporteur, other CHMP members, WHO experts, as appropriate and the EMEA.
115	Receipt of draft list of questions (including the CHMP recommendation and scientific discussion) from the Rapporteur and Co-Rapporteur, as discussed with the peer reviewers, by CHMP members, WHO Experts as appropriate, and the EMEA.
120	Adoption of the list of questions, overall conclusions and review of the scientific data by the CHMP. The EMEA sends these to the applicants and WHO Experts, as appropriate. Deadline for adoption of a request for a good manufacturing practice (GMP) or good clinical practice (GCP) inspection by the CHMP, if necessary, and start of inspection procedure.

The 'clock' is stopped at day 120. By analogy to the evaluation of centralised marketing authorisation applications, the same rules apply with regards the time allowed for applicants to respond to the list of questions and list of outstanding issues ([EMEA/75401/2006 Rev. 2](#)).

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

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

Day	Action
150	Receipt of joint response assessment report from the Rapporteur and Co-Rapporteur by CHMP members and the EMEA. The EMEA 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 yet represent the position of CHMP. Inspection is carried out, if applicable.
170	Deadline for comments on joint assessment report from CHMP members and WHO Experts as appropriate. Responses are sent to the Rapporteur and Co-Rapporteur, the EMEA and other CHMP members.
180	CHMP discussion and decision on whether the applicant will need to attend an oral explanation. If an oral explanation is needed, the clock is stopped to allow the applicant to prepare. Deadline for submission of the final inspection report to EMEA, Rapporteur and Co-Rapporteur by the inspections team, if applicable.
181	Clock is restarted. Oral explanation takes place (if needed).
By 210	Final draft of SPC, labelling and package leaflet in English sent by the applicant to the Rapporteur and Co-Rapporteur, the EMEA and other CHMP members and WHO Experts, as appropriate. Adoption of CHMP scientific opinion and assessment report.

After adoption of a CHMP scientific opinion, the annexes to the opinion and European public assessment report on a scientific opinion in co-operation with WHO (EPAR) are prepared according to the following timetable:

Day	Action
By 240	The EMEA forwards the CHMP scientific opinion and its annexes to the applicant, the WHO, EU Member States, Norway and Iceland.

By 300	Finalisation of the EPAR in consultation with the Rapporteur, Co-Rapporteur and CHMP, and with the applicant to discuss issues related to commercial confidentiality.
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References:

- [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of co-operation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community](#)

22. When and how are the Rapporteur and Co-Rapporteur appointed?

For any scientific evaluation that forms part of a procedure, Rapporteurs are appointed to lead the evaluation. Rapporteurs are selected from among the CHMP members, including the co-opted and alternate members. Each Rapporteur is supported by an assessment team of assessors and experts.

In the pre-opinion phase of an application for a CHMP scientific opinion, two Rapporteurs are appointed – these are named the ‘Rapporteur’ and the ‘Co-Rapporteur’. Normally, the Rapporteur continues on as the leader in the post-opinion phase.

The appointment of the Rapporteur and Co-Rapporteur is made on the basis of criteria that ensure that scientific opinions are made objectively using the best available expertise in the European Economic Area (EEA). The appointment procedure for Rapporteurs, Co-Rapporteurs and their assessment teams is usually initiated seven months prior to the intended submission date of the application, with the actual appointment taking place one month later. Therefore, the deadline for applicants to send their letter of intent to submit an application under Article 58 of Regulation (EC) No. 726/2004 is seven months before the intended submission date.

Applicants are strongly advised to notify the EMEA of their intended submission date for their marketing authorisation applications. This date should be as realistic and as accurate as possible. This information is crucial to the EMEA and to the future appointed Rapporteurs and their assessment teams for the purposes of planning.

Applicants’ proposals or preferences for the appointment of Rapporteurs and Co-Rapporteurs cannot be considered.

Further information on the objective criteria and the procedure for the appointment of Rapporteurs and Co-Rapporteurs is provided in the EMEA paper [“CHMP Rapporteur/Co-Rapporteur Appointment: Principles, Objective Criteria and Methodology” \(EMEA/124066/2005\)](#).

References:

- [EMEA Paper “CHMP Rapporteur/Co-Rapporteur Appointment: Principles, Objective Criteria and Methodology” \(EMEA/124066/2005\)](#)
- [CHMP Rules of Procedure \(EMEA/CHMP/45110/2007\)](#)
- [Regulation \(EC\) No 726/2004 of the European Parliament and of the Council](#)
- [Notice to Applicants, Volume 2A, Notice to Applicants Chapter 4](#)

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

The EMEA has a list of experts that can be called upon by the CHMP when it needs specific expertise during the evaluation of an application. In addition, for applications evaluated under Article 58, experts and observers are identified by WHO and nominated in consultation with CHMP/EMEA Secretariat.

The EMEA or the CHMP identifies the need for specific expertise before a request for nomination is sent to WHO for WHO experts or observers. The expertise required varies according to the type of

medicinal product, application or therapeutic area that are subject to the evaluation in question. The EMEA informs applicants of which WHO experts and observers are appointed for an individual procedure.

WHO observers are WHO staff or experts who act as observers or peer reviewers in a specific file or WHO-appointed national drug regulatory authority (NDRA) representatives, who follow the evaluation carried out by the CHMP but do not take part of it. Experts and observers have no voting rights at the CHMP plenary meetings. The precise tasks and responsibilities of WHO experts on a particular procedure are decided on a case-by-case basis. They may be asked to provide comments on all CHMP documents, in the same way as CHMP members. They may also be invited to attend CHMP, working party and scientific advisory group discussions on products submitted for evaluation under Article 58.

All the experts must carry out their tasks and responsibilities in accordance with EMEA confidentiality agreements, in order to fully protect the confidentiality of the data submitted to them (see [EMEA Code of Conduct](#)). Prior to their appointment and participation in meetings, all experts are obliged to submit a completed and signed nomination form, public declaration of interests and confidentiality undertaking form and *curriculum vitae*. In addition, experts can only participate in discussions on products under the CHMP scientific opinion procedure to an extent that is defined by their individual level of risk, in accordance with the [EMEA 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 produced during the procedure, such as responses to lists of questions or lists of outstanding issues. The EMEA is responsible for forwarding the relevant documents circulated and adopted during the evaluation procedure to the appointed WHO observers, such as (Co-)Rapporteurs' assessment reports, CHMP lists of questions, working party reports, and CHMP lists of outstanding issues, as appropriate.

References:

- [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community](#)
- [The EMEA Code of Conduct](#)

24. 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. This is decided on a case-by-case basis, with consultation of the CHMP, the appointed (Co-) Rapporteur and if applicable, WHO. Applicants should provide justification and rationale for any requests for accelerated assessment at the time of the request for eligibility.

25. Is it possible to obtain a scientific opinion under Article 58 under conditional or exceptional circumstances?

Yes it is. Article 58 refers to the applicability of Article 9 of the same Regulation, which in turn refers to Article 14(7) and (8). The principles of a “centralised conditional marketing authorisation” or a “marketing authorisation under exceptional circumstances” can therefore apply to scientific opinions under Article 58.

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](#)

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

The eligibility request is free of charge and the same fees are applied for the assessment of products using Article 58 as for to the centralised procedure, since the same resources are needed. For more information, see question 10 of the EMEA Pre-Submission Procedural Advice, [What fee do I have to pay and how is the appropriate fee for my application calculated?](#)

In exceptional cases and when an opinion is required for imperative reasons of public health, total or partial fee exemptions may be granted by the EMEA's Executive Director on the recommendation of the CHMP. Fee waivers or fee reductions are granted after consultation of the CHMP.

Where an applicant disagrees on the classification of an application under one of the fee categories described in the Fee Regulation, an appeal should be sent to the Executive Director accompanied by the appropriate justification, as early as possible, and not later than three months prior to the anticipated date of submission of the application. The Executive Director will take a decision following consultation with the CHMP.

References:

- [Regulation \(EC\) No 297/95, as amended](#)
- [Regulation \(EC\) No 141/2000](#)
- [Regulation \(EC\) No 2049/2005](#)
- [Centralised Procedure, the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 4](#)

27. 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 countries where the medicinal product is intended to be used.

The detailed description of the pharmacovigilance system needs to be submitted at time of application in module 1.8.1. An RMP should also be submitted in module 1.8.2 for the following types of application:

- products containing a new active substance;
- similar biological medicinal products;
- generic or hybrid medicinal products where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product;
- new dosage forms, routes of administration or manufacturing process of a biotechnologically-derived product;
- when there is a significant change in indication.

For all other type of applications, the need for a RMP submission should be checked well ahead of the submission with the EMEA.

Additional risk minimisation measures are required in situations when positive benefit/risk would not be achievable without them. Therefore, no positive Article 58 opinion can be adopted in such a situation.

Opinion Holder, in agreement with the competent authorities of the countries where the product is marketed, should inform the EMEA of any deviation to the submitted description of the Pharmacovigilance system and Risk Management Plan, and should provide the reason for such deviations. The CHMP may revise its opinion based on this information.

References:

- [Volume 9A of The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use](#)

28. Do applicants need to provide an environmental risk assessment in the target markets?

No, an environmental risk assessment (ERA) is not needed for applications under Article 58. However, applicants are encouraged to provide a justification for the lack of an ERA in the application at the time of submission, as appropriate.

For information on the environmental risk assessment see [Guideline on the environmental risk assessment of medicinal products for human use \(EMA/CHMP/SWP/4447/00\)](#).

29. What information should be provided on the manufacturer in an application?

In the notification of intention to submit, applicants should mention the names, contact points and addresses of the proposed manufacturers of the active substances and finished product. The sequence of all different sites involved should be clearly described in a flowchart.

In the application form, applicants should list the drug products under section 2.5.2 Batch control/Testing arrangements, and all manufacturers involved in all steps of the manufacturing of each active substance in section 2.5.3 Manufacturer(s) of the active substance(s).

During the 210-day review, the addition of a new manufacturing site or a change to the steps of manufacture or batch release described in the application form are not permitted. Such changes should be submitted as variation applications after the adoption of the scientific opinion.

Manufacturing sites:

The information on manufacturing sites submitted in Module 1.2 of the application must be consistent with module 3. All the manufacturing/batch release sites mentioned in module 3 must be listed in Module 1.2 and the activities carried out at each.

All sites involved in the production of the finished medicinal product and of the active substance should be described (name and detailed address, including building reference) in the application form of for a Article 58 Scientific Opinion together with a description of the steps performed. This should include:

- active substance manufacture
- bulk medicinal product manufacture
- diluent/solvent manufacture (if any)
- manufacture of any other associated medicinal product
- finished product manufacture and packaging
- any contract manufacturing sites
- any contract laboratories used for testing the finished product

For third country manufacturers, information about any previous EEA inspection in the last 2-3 years (with, if possible, a copy of the inspection report) and/or any planned EEA inspection(s) should be provided and should include details of the inspection dates, product category inspected and the name of the inspecting competent authority.

The following documents should be attached to the application form:

For all sites in the EEA, other than active substance manufacturers, copies of the "Manufacturing Authorisation" authorising the sites involved in the manufacture, importation, control and /or testing and Qualified Person release of batches of the medicinal product.

For all sites other than active substance manufacturers, located in third countries where a Mutual Recognition Agreement is in place, a MRA certificate, not older than 3 years, from the local competent authority that carried out the inspection and/ or a GMP certificate from the EEA inspecting competent authority if the site has been inspected by an EEA competent authority in the last 2-3 years.

For all sites other than active substance manufacturers, located in third countries with no Mutual Recognition Agreement, GMP certificate from the EEA inspecting competent authority if the site has been inspected by an EEA competent authority in the last 2-3 years.

For the sites that have not been inspected by an EEA competent authority in the last 2-3 years, it might be useful to provide copy of the annual registration or other document from the local competent authority demonstrating that the site is authorised for manufacture of the product/pharmaceutical form. A flow-chart describing all the main steps involved in the manufacture of the active substance and finished product.

A full justification on public health and/or technical grounds of any proposed multiple importing and batch release sites.

A document identifying the contact person responsible for any quality issues including its contact details.

Product defects and recalls:

The Opinion Holder should report to the competent authorities of the countries where the product is marketed and inform the EMEA about any defect in a medicinal product that could result in a recall or abnormal restriction in supply, together with the corrective actions proposed. In cases where the quality issues cannot be resolved, the CHMP may revise its opinion.

References:

- [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community](#)
- [Directive 2003/94/EC](#)
- [Directive 2001/83/EC](#)

30. 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 need testing before they are released for sale, if it would be in the interest of public health. Testing may be required for a live vaccine, an immunological product or a medicinal product derived from human blood or human plasma.

If testing is needed, the opinion holder will be requested to submit samples from each batch of the bulk or medicinal product before release onto the market for testing by an EU official medicines control laboratory (OMCL). A batch of a medicinal product must not be placed on the market until 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.

EU OMCLs are appointed by the European Directorate for the Quality of Medicines (EDQM) based on their competencies and workload. The CHMP provides list of key tests to be carried out by an EU OMCL as part of the scientific opinion. The OMCL should complete testing within 60 days after they have received the sample. If the product is compliant, the EDQM provides a European Community certificate of batch compliance to the applicant, who then provides the competent authority of the international area with a copy of the certificate for their formal acceptance.

References

- [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community](#)
- [News of the European Directorate for the Quality of Medicines - Pharmacopoeia on the WWWEU Control Authority Certification of compliance](#)

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

The same principles apply for good manufacturing practice (GMP) and good clinical practice (GCP) inspections for evaluations under Article 58 as for the evaluation of a centrally medicinal product. For details, see [question 28](#) and of the EMEA Pre-submission guidance document.

32. What is the fee for an inspection?

A separate, full inspection flat rate fee of €18,900 is charged for each distinct inspection of an individual site. Additional fees may be charged for activities on the same site that require a separate inspection and also for each contract manufacturing site and contract testing laboratory that needs to be inspected in connection with an application.

For inspections outside the Community, 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.

For more information on inspection fees, please see Annex IV of the [Rules for the implementation of Regulation \(EC\) No 297/95 as amended on fees payable to the European Medicines Agency and other measures \(Annex IV\): "Policy on financial transactions and payments for inspections requested by the CHMP or CVMP."](#)

References:

- [Regulation \(EC\) No 297/95, as amended](#)

33. How are active substance master files submitted?

ASMFs are needed for active substances that are prepared in accordance with the published [guidelines on ASMF](#). 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.

Applicants should refer to the Guideline on Active Substance Master File Procedure (CPMP/QWP/227/02) for information on what to send 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 to the EMEA, the Rapporteur and the Co-Rapporteur at the same time as the main application.

Please note that the applicant should include a commitment to inform the EMEA 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.

If the applicant wishes to use existing vaccine antigen master file (VAMF) or plasma master file (PMF) certificates in the application, it will be required to provide the valid VAMF or PMF certificate of compliance to Community legislation and accompanying evaluation reports together with the respective VAMF or PMF data.

References:

- [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community](#)
- [Guideline on Active Substance Master File Procedure \(CPMP/QWP/227/02 \)](#)
- [Annex I to the Directive 2001/83/EC, as amended](#)

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

If a 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, as amended. 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” and its updates.

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 to back up this compliance in module 3.2 of the dossier, 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 as amended, 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.

References:

- [Directive 2001/83/EC, as amended](#)
- [Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products \(EMEA/410/01\)](#)

35. Is there a European decision-making process after adoption of a scientific opinion?

There is no European decision-making process after adoption of a scientific opinion, since the purpose of opinions under Article 58 is to allow the evaluation of medicinal products for use exclusively in markets outside the Community.

References:

- [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community](#)

36. Is a European public assessment report published following a scientific opinion under Article 58?

Yes, a European public assessment reports (EPAR) is published following an opinion under Article 58, as for all products assessed by the CHMP. In the case of Article 58 opinions, it is known as a ‘European public assessment reports on a scientific opinion in co-operation with WHO (EPAR)’. The EPAR is published by day 300.

The EPAR reflects the scientific conclusions reached by the CHMP at the end of the evaluation process. The legal basis for its creation and availability is contained in Article 13(3) of Regulation

(EC) No 726/2004, by analogy. It is made available by the EMEA for information to the public, after deletion of commercially confidential information.

The EPAR is updated throughout the opinion period as changes to the original terms and conditions of the opinion are made, such as variations, pharmacovigilance issues and changes to specific obligations. EPARs also contain a summary written in a manner that is understandable by the public.

Other types of EPAR may also be published following the withdrawal of an application of a scientific opinion or following a negative scientific opinion. In such cases, the basis for publication is Articles 11 and 12 of Regulation (EC) No 726/2004, by analogy.

References:

- [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of co-operation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community](#)
- [Regulation \(EC\) No 726/2004](#)

37. Can the EMEA certify scientific opinions under Article 58?

The current WHO certification scheme allows for a Certificate of a Medicinal Product to be issued for a product that has received a positive CHMP scientific opinion under Article 58. The certificate certifies that the medicinal product has been evaluated for quality, safety and efficacy by the EMEA.

As for centrally authorised products, the EMEA issues these certificates upon request from the opinion holder.

For more information regarding certificates please see the [Inspections Homepage On Certificates](#).

References:

- [Guideline on procedural aspects regarding a CHMP scientific opinion in the context of co-operation with the World Health Organization \(WHO\) for the evaluation of medicinal products intended exclusively for markets outside the Community](#)
- [Regulation \(EC\) No 726/2004](#)

38. What happens after the opinion?

In some cases, the CHMP concludes that a medicinal product is only approvable on the condition that certain data are provided after the opinion. In these cases, the data requested should be submitted within the timeframe agreed with the CHMP and the applicant.

Any data submitted as part of post-opinion follow-up are evaluated by the CHMP, and the opinion holder is informed of the outcome. If the outcome requires an update of the CHMP opinion, the opinion holder will be requested to submit an application for a variation to the opinion within an agreed timeframe.

If any post-opinion commitments are not met, the CHMP can revise its opinion after consulting the WHO. In these cases, the revised opinion will be based on the re-assessment of the benefit/risk profile of the product.

All serious adverse events should be recorded by the opinion holders and reported to the EMEA and the competent authorities of the countries where the product is marketed within the time frames and format recommended by the International Conference on Harmonisation (ICH).

Furthermore, the opinion holders are required to submit **periodic safety update reports** (PSURs) on their product. These are reports on the worldwide safety experience of a medicinal product that are

submitted to the (Co-) Rapporteurs and the EMEA at defined time points after the opinion. PSURs include a succinct summary on the product's safety, together with a critical evaluation of the benefit/risk balance of the product in the light of any new information, indicating whether further investigation is needed and whether changes should be made to the opinion.

To keep the opinion valid throughout the life of a medicinal product, the opinion holder shall reflect any technical and scientific progress. Any amendments to the opinion that may be required need to be approved by the EMEA in collaboration with the WHO via **variation procedures**. By analogy, the same categories of variations apply for opinions under Article 58 as for centralised marketing authorisations, with the same data requirements.

References:

- [Regulation \(EC\) No 726/2004, Article 24\(3\)](#)
- [Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, ICH E2C](#)
- [Volume 9A of the Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use](#)
- [Notice to Applicants Volume 2A, Chapter 5 "Variations"](#)