EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

02 May 2013
EMA/599941/2012

Procedural advice on publication of information on negative opinions and refusals of marketing authorisation applications for human medicinal products

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

Table of contents

1. Introduction

This paper describes the documents to be published following negative opinions and refusals of marketing authorisation applications for human medicinal products.

This document updates information of the reflection paper on the publication of information on negative opinions and refusals of marketing authorisation applications for human medicinal products adopted by the European Medicines Agency (EMA) in September 2006. It takes into account changes in EMA communication practices for certain types of applications, new guidance from the Heads of Medicines Agencies (HMA) and the EMA on the identification of personal data and commercially confidential information in marketing authorisation applications.[1,2]

2. Legal basis and scope

The legal basis for the publication of documents on the refusal of an application for a marketing authorisation for human medicines is Article 12 (3) of Regulation (EC) 726/2004, which states that:

"Information about all refusals and the reasons for them shall be made publicly accessible."

The EMA therefore publishes documents reflecting the evaluation of new applications for marketing authorisations which have received a negative opinion by the CHMP.

In September 2006, on the basis of Article 80 of Regulation (EC) No 726/2004[3], the EMA Management Board extended the publication requirement to negative opinions on applications for extension of indication.

In addition, the paper covers the publication of documents following the refusal for other variations as well as extension applications. The principle is that the same level of transparency is applied to refused applications as is applied to applications that receive a positive opinion. This means that a document (e.g. an assessment report) that would have been published for an application that received a positive opinion will also be published in the event of a refusal.

The deletion of commercially confidential information referred to in this paper is based on the two HMA/EMA guidance documents adopted in March 2012, the provisions of which are applicable to EMA publications on negative opinions and refusals.

3. Documents to be made available to the public

3.1. Negative opinion and refusal of marketing authorisation applications without re-examination

The EMA will announce the negative opinion on new marketing authorisation applications and extension of indication applications in the CHMP meeting highlights published on the EMA website.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf
[2] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124537.pdf
[3] Article 80 of Regulation (EC) No 726/2004: "To ensure an appropriate level of transparency, the Management Board, on the basis of a proposal by the Executive Director and in agreement with the Commission, shall adopt rules to ensure the availability to the public of regulatory, scientific or technical information concerning the authorisation or supervision of medicinal products which is not of a confidential nature."

Question-and-answer (Q&A) document

The EMA will routinely publish Q&A documents following a negative opinion on new marketing authorisation applications and extension of indication applications, as these are the applications that are most likely to generate interest among stakeholders and the general public.

The Q&A document contains information in lay language on the scientific assessment of the medicine and reflects the grounds for opinion.

The Q&A document is first published in English at the time of CHMP opinion, with translations in all official languages of the EU published at the time of the publication of the refusal assessment report.

The EMA reserves the right to publish Q&A documents for other variation applications including extension applications should it be considered necessary or of interest to the public.

A template for Q&As is included in Annex I of this document.

Refusal assessment reports

The EMA will publish the CHMP refusal assessment report for all applications for new marketing authorisations and extension of indication applications. The CHMP refusal assessment reports will also be published for other variations as well as extension applications in cases where an assessment report would have been published for a positive opinion.[4]

Prior to publication of any refusal assessment report the EMA will liaise with the applicant to delete commercially confidential information. Guidance from the HMA/EMA document adopted in March 2012 should be followed.[5]

The refusal assessment report will be published within four weeks of a European Commission decision. In cases where the European Commission does not issue a decision, the refusal assessment report will be published no later than three months after the CHMP opinion.

Procedural steps document

A document entitled 'Procedural steps taken and scientific information after authorisation' is available on the EMA website for all centrally authorised medicines and it outlines the regulatory procedures that have taken place since the authorisation of the medicine. The procedural steps document should contain information on any variation application including extension applications.

The inclusion of all negative opinions issued in the procedural steps document is an important transparency tool providing information on the regulatory history of the product and the scientific evaluations that have taken place.

Refusal EPARs

Refusal European public assessment report (EPAR) is a term that describes all the relevant documents published following a negative opinion on a new marketing authorisation application: Q&A and refusal assessment report. Refusal EPARs only apply to negative opinions on a new marketing authorisation application. In case of a negative opinion of a variation application, the Q&A, if available, and refusal assessment report together with the updated procedural steps document will be published within the existing EPAR page of the authorised medicinal product.

[4] Information on the publication of assessment reports for positive opinions can be found in the EMA SOP on updating of the European Public Assessment Report for a human medicinal product (SOP/H/3012)

[5] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf

3.2. Negative opinion and refusal of marketing authorisation applications which is followed by a re-examination

If the CHMP issues a negative opinion on a new marketing authorisation application, an extension of marketing authorisation or a variation application, the applicant may request in writing a re-examination of the opinion within 15 days after the receipt of the opinion (as per Article 9 (2) of Regulation (EC) No 726/2004[6]).

Documents to be published in case of negative opinion following the re-examination procedure:

Question-and-answer (Q&A) document

The Q&A document that was published following the initial negative opinion will be updated to reflect the final CHMP negative opinion on the re-examination procedure (see templates annexed).

The Q&A document is first published in English at the time of CHMP opinion, with translations in all official languages of the EU published at the time of the publication of the refusal assessment report. Publication will be within four weeks of a European Commission decision if a decision is expected, or no later than three months after CHMP opinion when no decision is expected.

A template for Q&As is included in Annex II of this document.

Refusal assessment report

The refusal assessment report of the initial opinion will be updated to clearly reflect the re-examination and will be published within four weeks of a European Commission decision if a decision is expected, or no later than three months after CHMP opinion on the re-examination when no decision is expected.

Procedural steps document

For an authorised product, the procedural steps document will contain information on the outcome of any re-examination that is carried out.

The inclusion of all re-examination opinions issued in the procedural steps document is an important transparency tool providing information on the regulatory history of the product and the scientific evaluations that have taken place.

Documents to be published after positive opinion following the re-examination procedure:

Question-and-answer (Q&A) document

The Q&A document that was published following the initial negative opinion will be updated to reflect the final CHMP positive opinion following the re-examination procedure (see templates annexed).

Assessment report

The refusal assessment report of the initial opinion will be updated to clearly reflect the re-examination and will be re-named “assessment report”. It will be published within four weeks of a European Commission decision if decision is expected.

[6] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726_cons/reg_2004_726_cons_en.pdf

Procedural steps document

The procedural steps document will contain information on the outcome of any re-examination that is carried out post-authorisation.

Summary of Opinion

In addition a summary of positive opinion will be published at the end of the CHMP meeting during which the positive opinion is adopted in addition to the updated Q&A document.

4. Table of documents to be published

4.1. For initial negative opinion / refusal of marketing authorisation applications

Type of application	Documents	Timing
Refused applications for a new marketing authorisation	Q&A	At the time of CHMP opinion
	Assessment report	Within four weeks of a European Commission decision
Negative opinion on applications for extension of indication	Q&A	At the time of CHMP opinion
	Assessment report	No later than three months after CHMP opinion
	Updated procedural steps document	No later than three months after CHMP opinion
Negative opinion on other refused applications**	Assessment report*	No later than three months after CHMP opinion
	Updated procedural steps document	No later than three months after CHMP opinion

* To be published in cases where an assessment report would have been published for a positive opinion.
** Q&As and press releases will be considered if there is public interest.

4.2. Following a re-examination

Type of application	Documents	Timing
Refused applications for a new marketing authorisation	Updated Q&A	At the time of CHMP re-examination opinion
	Updated assessment report	Within four weeks of a European Commission decision
Negative opinion on applications for extension of indication	Updated Q&A	At the time of CHMP re-examination opinion
	Updated assessment report	No later than three months after CHMP re-examination opinion
	Updated procedural steps document	No later than three months after CHMP re-examination opinion
Negative opinion on other refused applications**	Updated assessment report*	No later than three months after CHMP re-examination opinion
	Updated procedural steps document	No later than three months after CHMP re-examination opinion

* To be published in cases where an assessment report would have been published for a positive opinion
**Q&As and press releases will be considered if there is public interest

5. Annexes

ANNEX I – Templates Question & Answer Document on recommendation for refusal

Ia – Refusal of the marketing authorisation:

Questions and answers

Refusal of the marketing authorisation for <X> (active substance/common name)

What is <X>?

What was <X> expected to be used for?

How is <X> expected to work?

What did the company present to support its application?

What were the CHMP's main concerns that led to the refusal?

What consequences does this refusal have for patients in clinical trials or compassionate use programmes?

<What is happening with <X> for <treatment/prevention/diagnosis> of <other diseases>>?

Refusal of a change to the marketing authorisation for <X> (active substance/common name)

What is <X>?

What was <X> expected to be used for?

How is <X> expected to work?

What did the company present to support its application?

What were the CHMP's main concerns that led to the refusal of the change to the marketing authorisation?

What consequences does this refusal have for patients in clinical trials or compassionate use programmes?

What is happening with <X> for <treatment/prevention/diagnosis> of <other diseases>?

ANNEX II – Templates Question & Answer Document for outcome of re-examination

The text should be based on the initial Q&A

IIa - Re-examination confirming the recommendation for refusal for marketing authorisation:

Questions and answers

Refusal of the marketing authorisation for <X> (active substance/common name)

Outcome of re-examination

What is <X>?

What was <X> expected to be used for?

How is <X> expected to work?

What did the company present to support its application?

What were the CHMP's main concerns that led to the refusal?

What consequences does this refusal have for patients in clinical trials or compassionate use programmes?

<What is happening with <X> for <treatment/prevention/diagnosis> of <other diseases>>?

IIb - Re-examination confirming the recommendation for refusal for change to the marketing authorisation:

Questions and answers

Refusal of a change to the marketing authorisation for <X> (active substance/common name)

Outcome of re-examination

What is <X>?

What was <X> expected to be used for?

How is <X> expected to work?

What did the company present to support its application?

What were the CHMP's main concerns that led to the refusal of the change to the marketing authorisation?

What consequences does this refusal have for patients in clinical trials or compassionate use programmes?

What is happening with <X> for <treatment/prevention/diagnosis> of <other diseases>?

IIc - Re-examination leading to a positive opinion on marketing authorisation:

Questions and answers

Positive opinion on the marketing authorisation for <X> (active substance/common name)

Outcome of re-examination

What is <X>?

What is <X> to be used for?

How does <X> work?

What did the company present to support its application?

What were the CHMP's main concerns that led to the initial negative opinion?

What happened during the re-examination?

What were the conclusions of the CHMP following the re-examination?

IId - Re-examination leading to a positive opinion on the change to the marketing authorisation:

Questions and answers

Positive opinion on the change to the marketing authorisation for <X> (active substance/common name)

Outcome of re-examination

What is <X>?

What is <X> to be used for?

How does <X> work?

What did the company present to support its application?

What were the CHMP's main concerns that led to the initial negative opinion?

What happened during the re-examination?

What were the conclusions of the CHMP following the re-examination?