European Medicines Agency

London, 6th January 2009
Doc. Ref. EMEA/75401/2006 Rev. 2

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

TIME ALLOWED FOR APPLICANTS TO RESPOND TO QUESTIONS AND ISSUES RAISED DURING THE ASSESSMENT OF NEW MARKETING AUTHORISATION APPLICATIONS IN THE CENTRALISED PROCEDURE

DISCUSSION CHMP	MARCH/APRIL 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	APRIL 2005 JULY 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 OCTOBER 2005
ADOPTION BY CHMP	23 FEBRUARY 2006
DATE FOR COMING INTO EFFECT	MARCH 2006
UPDATE OF EXISTING DOCUMENT BY CHMP	MAY/JUNE 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 JULY 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 SEPTEMBER 2008
ADOPTION BY CHMP	18 DECEMBER 2008
DATE FOR COMING INTO EFFECT	JANUARY 2009

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 60
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

TIME ALLOWED FOR APPLICANTS TO RESPOND TO QUESTIONS AND ISSUES RAISED DURING THE ASSESSMENT OF NEW MARKETING AUTHORISATION APPLICATIONS IN THE CENTRALISED PROCEDURE

TABLE OF CONTENTS

INTRODUCTION

There is clearly laid out in the Legislation a timetable of 210 days[1] for the evaluation of centralised marketing authorisation applications (MAAs). Clear "rules" are needed as to how long applicants may take to respond to questions/issues raised during the evaluation of such MAAs. This is important to ensure that the Committee for Medicinal Products for Human Use (CHMP) is consistent in dealing with applications; therefore a policy applicable to the evaluation of all new MAAs has been established. Such a policy should:

1. Enable applicants to have sufficient time to respond to questions and issues that have been identified through the assessment process, including requests from the CHMP for additional data and/or results from additional studies.
2. Avoid so-called "premature" applications (applications supplemented during the review period with substantial new data that should have been presented at the time of the initial application).
3. Enable the centralised procedure to run efficiently, balancing the needs of applicants to adequately address questions/issues with the requirements for regulators to assess applications in an efficient and timely manner.

Applicants are reminded that, in general, no substantial data derived from new studies should be introduced as part of the responses to the List of Questions (LoQs) or List of Outstanding issues (LoOIs) that were not specifically requested by the CHMP. However, new analysis might be included, such as follow-up data from previously submitted studies. This is particularly important at day 180 where assessment time is limited.

This document should be read in conjunction with the following guidelines:

- Guidance on the Rapporteurs meetings with applicants on the CHMP List of Questions (CPMP/2270/02): http://www.emea.europa.eu/pdfs/human/regaffair/227002en.pdf

- Guidance to applicants on CPMP oral explanations in relation to centralised applications (CPMP/2390/01 – rev.1): http://www.emea.europa.eu/pdfs/human/regaffair/239001en.pdf

GENERAL PRINCIPLES

The CHMP produces a LoQs at day 120. Applicants respond and the clock restarts on day 121. At day 180, the CHMP produces a joint assessment report with a LoOIs to be addressed by the applicant. At this point the CHMP will normally be considering the need for an oral explanation. The company would then prepare a written response to the LoOIs and prepare for the oral explanation if applicable.

To enable the centralised process to run efficiently, it is necessary to have an appropriate time period to allow companies to respond to the LoQs at day 120, coupled with a more streamlined process from day 180 to the opinion being adopted. At day 180, the procedure should run smoothly and rapidly to completion, commensurate with the limited assessment time available. In addition there would be greater opportunities for the applicant to receive feedback from the Rapporteur, Co-Rapporteur and the EMEA on the CHMP concerns and response strategy. The principles are as follows[2]:

- Prior to an application being submitted, it is recommended to have a **pre-submission meeting** with the applicant (please see the EMEA meeting guidance document http://www.emea.europa.eu/htms/human/presub/38271206en.pdf), at the EMEA and with the

[1] In accordance with Article 6(3) of Regulation (EC) No. 726/2004.
[2] For procedure handled under an accelerated timetable in accordance with Article 14(9) of Regulation (EC) No. 726/2004, the principles are described in http://www.emea.europa.eu/pdfs/human/euleg/41912705en.pdf

Rapporteur and Co-Rapporteur (usually via separate meetings), which will include a discussion of ongoing studies related to the claimed indication(s) including status of all ongoing studies from a safety point of view, when they will be available, and whether critical to the assessment of the dossier. The purpose of this meeting is to discuss the proposed contents of the application, so that the Rapporteur, Co-Rapporteur and the EMEA can be introduced to the file and can comment and advise if they feel that the application is considered to be "premature" or might benefit by including data from ongoing studies prior to the application being submitted. It is of course recognised that it is up to the applicant to decide when to file, and whether to accept the advice of the Rapporteurs. It is not the purpose of these meetings to offer scientific advice as alternative procedures are available for this.

- **In between the start of the centralised procedure evaluation and the adoption of the LoQs** (at day 120), applicants should refrain from contacting the Rapporteur/Co-Rapporteur to facilitate the review of the application[3].

- The **LoQs at day 120** should be responded to within 3 months. Applicants may request an additional period of up to 3-month for providing their responses by writing to the Chair of the CHMP outlining their reasons. This request will however only be considered by the CHMP if the applicant provides appropriate scientific justification. The CHMP will review the justification for the additional period (up to 3 months) for responding to the LoQs at its next scheduled plenary session following the receipt of the applicant's request and will only grant such requests, in the event that it is considered that this extension will enable the applicant to respond fully to the questions raised. Extensions beyond 6 months from the date of issue of the day 120 LoQs would not normally be accepted.

- Rapporteur, Co-Rapporteur and the EMEA should be available to meet applicants **after the day 120 LoQs** are issued, to clarify the intent behind the questions and explain the CHMP's concerns, as necessary (please also refer to the guidance on the Rapporteurs meetings with applicants on the CHMP List of Questions (CPMP/2270/02)[4]). If the applicant wishes, this could include comment on the approach the applicant proposes to take in responding to the questions as to whether they are correctly approaching the issues raised in the LoQs. It may be that this will require 1 or 2 sets of discussions, one to debrief the questions, the other prior to response (such meetings are not necessarily face-to-face meetings; these could be organised *via* the EMEA through teleconferencing or videoconferencing, if possible, and upon availability of Rapporteur/Co-Rapporteur). It is expected that applicants have considered/analysed the LoQs within their company/product team and identified relevant clarifications to be asked in advance of such meeting(s).

- Following the release of the **LoOIs at day 180**, applicants should respond in writing within 1-month. Only very limited new data derived from new studies would be acceptable at this point of the procedure as assessment time beyond day 180 is extremely limited. In exceptional circumstances, a 1-month extension in submission of the written responses may be granted only upon provision of appropriate scientific justifications to be reviewed and agreed upon by the CHMP. The request for an extension of the timeframe should be submitted as soon as possible and addressed to the CHMP Chairman. In case the LoOIs is to be addressed partly or completely as part of an oral explanation, this will normally be scheduled one month after the submission of the written responses. In preparation for such oral explanation, applicants are advised to consult the "Guidance to applicants on CPMP oral explanations in relation to centralised applications" (CPMP/2390/01 – rev.1): http://www.emea.europa.eu/pdfs/human/regaffair/239001en.pdf, as appropriate.

[3] Procedural advice to CHMP members – Annex 2 (http://www.emea.europa.eu/pdfs/human/regaffair/36194507en.pdf)
[4] http://www.emea.europa.eu/pdfs/human/regaffair/227002en.pdf

- Additional clock stops would not normally be permitted unless relating to issues of inspection (i.e. need for GCP or GMP inspection instigated by the CHMP) or need for additional expert input (i.e. SAG or ad-hoc expert group).

REFERENCES

- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (*Official Journal L 136, 30/4/2004 p. 1 - 33*): http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

- Consolidated Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended by Directive 2002/98/EC, Directive 2004/24/EC and Directive 2004/27/EC.: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/consol_2004/human_code.pdf

- Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (Official Journal L 159, 27/6/2003 p. 46 - 94): http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf