European Medicines Agency

London, 9th December 2008
Doc. Ref. EMEA/545180/2008

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

Table 1: Organisations that commented on the guidance as released for consultation

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	EFPIA	Belgium
2	LFB Biotechnologies	France

* no specific comments have been received

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Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW	OUTCOME
As compared to the previous version (EMEA/75401/2006 Rev 1), it appears that the hurdle for an extension of the response period following day 120 and particularly day 180 is being raised. EFPIA does not support these changes. A longer response time (but still within the maximum duration stipulated in the guideline) is sometimes necessary to provide better quality responses. A better quality response facilitates the subsequent review and increases efficiency in that way. The alternative would be a re-submission of the application which requires a lot of duplicate work by both applicant and reviewer. Efficiency is one of the three driving factors for the policy as outlined in the guideline, but re-submission is very inefficient. If there are going to be forced re-submissions due to exceeding the response period, then it is hoped that the re-submission application will be reviewed following an accelerated timetable. If the responding to a CHMP question is likely to take more than the recommended 3 and 1 month respectively, then the CHMP might consider proposing a post-approval commitment to avoid a time wasting re-submission altogether.	As part of improving consistency and efficiency of the review procedure and based on past experience, the Committee wishes to strengthen its approach when granting a 3-month extension at Day 120 and a 1-month extension at Day 180 in order to avoid routine extensions that in some cases have shown to be of no-added value. Indeed the Committee would like to review more carefully requests for timetable extension and limit these to cases where a true benefit for extending the timetable may be gained for the on-going review of a particular dossier. More attention will be paid to the applicant's argumentation when requesting extensions of timetable.

SPECIFIC COMMENTS ON TEXT

1. GUIDELINE SECTION TITLE

Line no.[1] + paragraph no.	Comment and Rationale	Outcome
Bullet 2 p. 3	We believe the guideline mistakenly assumes that the availability of any new data during the procedure implies that the original application was premature. It would be valuable to take a more balanced view of "new data", which takes into account that although an application is complete, it is not unusual that new data from further studies become available during the review and that such data might be helpful for the review. This appears to be already acknowledged later in the document where responses to LoOIs at day 180 are discussed (page 4, penultimate bullet, 2nd sentence).	The introduction has not been modified and does not assume that the availability of any new data during the procedure implies that the original application was premature. It emphasizes that unless CHMP has specific requests, no substantial data derive from new studies should be submitted.
Bullet 1 p. 3&4	The pre-submission meeting with the EMEA usually takes place 6-7 months before submission. Rapporteur and Co-Rapporteur are often not appointed at that time, so meetings with them take place even closer to the date of submission when the preparation for submission is at its final stages. For the applicant the objective of all pre-submission meetings is to present the dossier, outline the key studies and high level results. At this late stage, the objective should not be to assess whether the application is premature. The EMEA guidance on pre-submission meetings indicates they are considering the introduction of a "'regulatory-strategy"' meeting 18-24 months in advance of the submission date (bridging meeting between scientific advice , interim analysis of phase II results and actual	Comments acknowledged but not relevant in the context of this guidance.

[1] Where applicable

	preparation of the application). This would be the right time to discuss the content of the dossier in more detail, and the possibility of having this kind of a meeting is highly supported.	
Bullet 2 p. 4	Day 80 draft assessment reports (ARs) are sometimes delayed and the applicant should be allowed to inquire about progress in assessment if the reports are overdue. Timely and simultaneous provision of draft ARs helps the applicant to prepare a high quality and timely response to the Day 120 List of Questions especially if the opinion of Rapporteur and Co-Rapporteur is divergent. If important unexpected new information, that might affect the Rapporteur's recommendation to the CHMP, first emerges during day 0-120 (e.g. data from ongoing studies) then it might be more efficient if the Rapporteurs learn about that without delay. Rapporteurs should not be discouraged by this provision to ask for relatively simple clarification during day 0 and 120 that might speed-up the assessment considerably if provided during the original assessment. Examples are questions about the exact location of certain data, the meaning of terminology not understood by the reviewer, or requests for a slightly different presentation of the information provided.	Comments rejected as this guidance is not the place to describe interactions between applicants, Rapporteurs and EMEA Product Team Leader. Note: This bullet point deals with contact of the Rapporteur by the applicant. It does not deal with the contact of the applicant by the Rapporteur – the possibility for such contact remains unchanged. However a footnote has been added providing cross reference to Procedural advice to CHMP members – Annex 2 (http://www.emea.europa.eu/pdfs/human/regaffair/36194507en.pdf) where such interactions are described.
Bullet 3 p. 4	Whether an additional period of up to 3 months is granted for responding to LoQs is based only on appropriate scientific justification. However there maybe some other valid reasons for requesting extra time to respond to the LoQs. Resource constraints should also be considered a valid reason for example under the following circumstances: • SMEs may be disadvantaged if the same timelines were to apply to them • Larger companies may have several global marketing applications ongoing in parallel each following process timelines not entirely under the applicant's control. Questions from different agencies might be received at the same time and compete for the same resources and therefore responses can not be written without extra time. Some activities may be carried out by third parties in different parts of the globe, adding to the	The deletion of "scientific" justification has been rejected as the CHMP wishes to receive the scientific rationale for extending the timetable. Nevertheless nothing prevents the applicant to broaden his rationale for extending the timetable but that may not be taken into consideration by the CHMP. Clarification has been added regarding how long the CHMP might take to respond to 3-month extension requests.

	timelines. • For products developed by alliances or joint ventures, additional time may be required in order to get all parties' input into the responses • Some additional analyses of clinical data can be rather labour intensive, e.g. if recoding of all CRFs is required. It would be helpful to clarify in this revision to the guidance how quickly the CHMP might respond to a request to extend beyond 3 months, so that the applicant can plan its work appropriately.	
Bullet 5 p. 4	With regards to the timelines after day 180 it is important to maintain some flexibility. The one month extension should not be granted only in exceptional circumstances or only with the provision of appropriate scientific justifications. As above other reasons may justify an extension of time. In the context of an oral explanation, certain non-scientific aspects are outside of the applicants' control (e.g. availability of external experts) and it is important that the Company's reasons on these practical aspects are considered by the CHMP in order to allow applicants to prepare in the best possible manner. It is stated that if an oral explanation is needed for answering the LoOIs it will normally be scheduled one month after the submission of the written responses. However, it may be possible to prepare the oral explanation sooner then 1 month and therefore there should be an opportunity to present earlier then 1 month. This could help move the assessment quicker and smoother through this part of the process. It would be helpful to clarify in this revision to the guidance how quickly the CHMP chairman might respond to a request to extend beyond 1 month, so that the applicant can plan its work appropriately.	The deletion of "scientific" justification has been rejected as the CHMP wishes to receive the scientific rationale for extending the timetable. A one month extension of timeframe will be granted in exceptional circumstances or on the provision of appropriate scientific justification. Further extensions will only be permitted relating to issues of inspection or need for additional expert input. Nevertheless nothing prevents the applicant to broaden his rationale for extending the timetable but that may not be taken into consideration by the CHMP. This will be dealt on a case by case basis, in accordance with agreed timetables / meeting dates. This will depend on when and how quickly the request is submitted. If the request is already submitted before the close of the CHMP meeting at which the List of Outstanding issues is adopted, a response will be provided directly after the meeting. If the request is received after the end of the CHMP meeting, the CHMP will review the provided justification and an outcome will be communicated to the applicant following the next CHMP meeting.
Bullet 6	It is unclear what is meant by "need for additional expert input" and	Clarification has been included in the guideline. Duration of clock stop will be

p. 4	what could be the duration of the clock stop. A maximum of 1-month additional clock stop in this case is regarded reasonable.	dealt on a case by case basis.